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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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# PRIORITY DOCUMENT

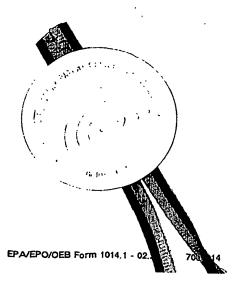
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R C van Dijk





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Si aucun titre n'est indiqué se referer à la description.)

Single nucleotide polymorphisms as predictive diagnostics for adverse drug reactions (ADR and drug efficacy)

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# Single Nucleotide Polymorphisms as Predictive Diagnostics for Adverse Drug Reactions (ADR) and Drug Efficacy

### Technical Field

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This invention relates to genetic polymorphisms useful for assessing the response to lipid lowering drug therapy and adverse drug reactions of those medicaments. In addition it relates to genetic polymorphisms useful for assessing cardiovascular risks in humans, including, but not limited to, atherosclerosis, ischemia/reperfusion, hypertension, restenosis, arterial inflammation, myocardial infarction, and stroke. Specifically, the present invention identifies and describes gene variations which are individually present in humans with cardiovascular disease states, relative to humans with normal, or non-cardiovascular disease states, and/or in response to medications relevant to cardiovascular disease. Further, the present invention provides methods for the identification and therapeutic use of compounds as treatments of cardiovascular disease or as prophylactic therapy for cardiovascular diseases. Moreover, the present invention provides methods for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of cardiovascular disease, and for monitoring the efficacy of compounds in clinical trials. Still further, the present invention provides methods to use gene variations to predict personal medication schemes omitting adverse drug reactions and allowing an adjustment of the drug dose to achieve maximum benefit for the patient. Additionally, the present invention describes methods for the diagnostic evaluation and prognosis of various cardiovascular diseases, and for the identification of subjects exhibiting a predisposition to such conditions.

## Background of the Invention

Cardiovascular disease is a major health risk throughout the industrialized world.

Cardiovascular diseases include but are not limited by the following disorders of the heart and the vascular system: congestive heart failure, myocardial infarction,

atherosclerosis, ischemic diseases of the heart, coronary heart disease, all kinds of atrial and ventricular arrhythmias, hypertensive vascular diseases and peripheral vascular diseases.

Heart failure is defined as a pathophysiologic state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirement of the metabolizing tissue. It includes all forms of pumping failure such as high-output and low-output, acute and chronic, right-sided or left-sided, systolic or diastolic, independent of the underlying cause.

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Myocardial infarction (MI) is generally caused by an abrupt decrease in coronary blood flow that follows a thrombotic occlusion of a coronary artery previously narrowed by arteriosclerosis. MI prophylaxis (primary and secondary prevention) is included as well as the acute treatment of MI and the prevention of complications.

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Ischemic diseases are conditions in which the coronary flow is restricted resulting in an perfusion which is inadequate to meet the myocardial requirement for oxygen. This group of diseases include stable angina, unstable angina and asymptomatic ischemia.

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Arrhythmias include all forms of atrial and ventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation, atrio-ventricular reentrant tachycardia, preexitation syndrome, ventricular tachycardia, ventricular flutter, ventricular fibrillation) as well as bradycardic forms of arrhythmias.

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Hypertensive vascular diseases include primary as well as all kinds of secondary arterial hypertension (renal, endocrine, neurogenic, others).

Peripheral vascular diseases are defined as vascular diseases in which arterial and/or venous-flow-is-reduced resulting in an imbalance between blood supply and tissue oxygen demand. It includes chronic peripheral arterial occlusive disease (PAOD),

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acute arterial thrombosis and embolism, inflammatory vascular disorders, Raynaud's phenomenon and venous disorders.

Atherosclerosis, the most prevalent of vascular diseases, is the principal cause of heart attack, stroke, and gangrene of the extremities, and thereby the principal cause of death. Atherosclerosis is a complex disease involving many cell types and molecular factors (for a detailed review, see Ross, 1993, Nature 362: 801-809 and Lusis, A. J., Nature 407, 233-241 (2000)). The process, in normal circumstances a protective response to insults to the endothelium and smooth muscle cells (SMCs) of the wall of the artery, consists of the formation of fibrofatty and fibrous lesions or plaques, preceded and accompanied by inflammation. The advanced lesions of atherosclerosis may occlude the artery concerned, and result from an excessive inflammatory-fibroproliferative response to numerous different forms of insult. For example, shear stresses are thought to be responsible for the frequent occurrence of atherosclerotic plaques in regions of the circulatory system where turbulent blood flow occurs, such as branch points and irregular structures.

The first observable event in the formation of an atherosclerotic plaque occurs when blood-borne monocytes adhere to the vascular endothelial layer and transmigrate through to the sub-endothelial space. Adjacent endothelial cells at the same time produce oxidized low density lipoprotein (LDL). These oxidized LDLs are then taken up in large amounts by the monocytes through scavenger receptors expressed on their surfaces. In contrast to the regulated pathway by which native LDL (nLDL) is taken up by nLDL specific receptors, the scavenger pathway of uptake is not regulated by the monocytes.

These lipid-filled monocytes are called foam cells, and are the major constituent of the fatty streak. Interactions between foam cells and the endothelial and SMCs which surround them lead to a state of chronic local inflammation which can eventually lead to smooth muscle cell proliferation and migration, and the formation of a fibrous

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plaque. Such plaques occlude the blood vessel concerned and thus restrict the flow of blood, resulting in ischemia.

Ischemia is a condition characterized by a lack of oxygen supply in tissues of organs due to inadequate perfusion. Such inadequate perfusion can have number of natural causes, including atherosclerotic or restenotic lesions, anemia, or stroke, to name a few. Many medical interventions, such as the interruption of the flow of blood during bypass surgery, for example, also lead to ischemia. In addition to sometimes being caused by diseased cardiovascular tissue, ischemia may sometimes affect cardiovascular tissue, such as in ischemic heart disease. Ischemia may occur in any organ, however, that is suffering a lack of oxygen supply.

The most common cause of ischemia in the heart is atherosclerotic disease of epicardial coronary arteries. By reducing the lumen of these vessels, atherosclerosis causes an absolute decrease in myocardial perfusion in the basal state or limits appropriate increases in perfusion when the demand for flow is augmented. Coronary blood flow can also be limited by arterial thrombi, spasm, and, rarely, coronary emboli, as well as by ostial narrowing due to luctic aortitis. Congenital abnormalities, such as anomalous origin of the left anterior descending coronary artery from the pulmonary artery, may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults. Myocardial ischemia can also occur if myocardial oxygen demands are abnormally increased, as in severe ventricular hypertrophy due to hypertension or aortic stenosis. The latter can be present with angina that is indistinguishable from that caused by coronary atherosclerosis. A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxy-hemoglobin, is a rare cause of myocardial ischemia. Not infrequently, two or more causes of ischemia will coexist, such as an increase in oxygen demand due to left ventricular hypertrophy and a reduction in oxygen supply secondary to coronary atherosclerosis.

The foregoing studies are aimed at defining the role of particular gene variations presumed to be involved in the misleading of normal cellular function leading to cardiovascular disease. However, such approaches cannot identify the full panoply of gene variations that are involved in the disease process.

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At present, the only available treatments for cardiovascular disorders are pharmaceutical based medications; that are not targeted to an individual's actual defect; examples include angiotensin converting enzyme (ACE) inhibitors and diuretics for hypertension, insulin supplementation for non-insulin dependent diabetes mellitus (NIDDM), cholesterol reduction strategies for dyslipidaemia, anticoagulants, β blockers for cardiovascular disorders and weight reduction strategies for obesity. If targeted treatment strategies were available it might be possible to predict the response to a particular regime of therapy and could markedly increase the effectiveness of such treatment. Although targeted therapy requires accurate diagnostic tests for disease susceptibility, once these tests are developed the opportunity to utilize targeted therapy will become widespread. Such diagnostic tests could initially serve to identify individuals at most risk of hypertension and could allow them to make changes in lifestyle or diet that would serve as preventative measures. The benefits associated by coupling the diagnostic tests with a system of targeted therapy could include the reduction in dosage of administered drugs and thus the amount of unpleasant side effects suffered by an individual. In more severe cases a diagnostic test may suggest that earlier surgical intervention would be useful in preventing a further deterioration in condition.

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It is an object of the invention to provide genetic diagnosis of predisposition or susceptibility for cardiovascular diseases. Another related object is to provide treatment to reduce or prevent or delay the onset of disease in those predisposed or susceptible to this disease. A further object is to provide means for carrying out this diagnosis.

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Accordingly, a first aspect of the invention provides a method of diagnosis of disease in an individual, said method comprising determining one, various or all genotypes in said individual of the genes listed in the Examples.

In another aspect, the invention provides a method of identifying an individual predisposed or susceptible to a disease, said method comprising determining one, various or all genotypes in said individual of the genes listed in the Examples.

The invention is of advantage in that it enables diagnosis of a disease or of certain disease states via genetic analysis which can yield useable results before onset of disease symptoms, or before onset of severe symptoms. The invention is further of advantage in that it enables diagnosis of predisposition or susceptibility to a disease or of certain disease states via genetic analysis.

The invention may also be of use in confirming or corroborating the results of other diagnostic methods. The diagnosis of the invention may thus suitably be used either as an isolated technique or in combination with other methods and apparatus for diagnosis, in which latter case the invention provides a further test on which a diagnosis may be assessed.

The present invention stems from using allelic association as a method for genotyping individuals; allowing the investigation of the molecular genetic basis for cardiovascular diseases. In a specific embodiment the invention tests for the polymorphisms in the sequences of the listed genes in the Examples. The invention demonstrates a link between this polymorphisms and predispositions to cardiovascular diseases by showing that allele frequencies significantly differ when individuals with "bad" serum lipids are compared to individuals with "good" scrum levels. The meaning of "good and bad" serum lipid levels is defined in Table 1a.

Certain disease states would benefit, that is to say the suffering of the patient may be reduced or prevented or delayed, by administration of treatment or therapy in

advance of disease appearance; this can be more reliably carried out if advance diagnosis of predisposition or susceptibility to disease can be diagnosed.

## Pharmacogenomics and adverse drug reactions

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Adverse drug reactions (ADRs) remain a major clinical problem. A recent metaanalysis suggested that in the USA in 1994, ADRs were responsible for 100 000 deaths, making them between the fourth and sixth commonest cause of death (Lazarou 1998, J. Am. Med. Assoc. 279:1200). Although these figures have been heavily criticized, they emphasize the importance of ADRs. Indeed, there is good evidence that ADRs account for 5% of all hospital admissions and increase the length of stay in hospital by two days at an increased cost of ~\$2500 per patient. ADRs are also one of the commonest causes of drug withdrawal, which has enormous financial implications for the pharmaceutical industry. ADRs, perhaps fortunately, only affect a minority of those taking a particular drug. Although factors that determine susceptibility are unclear in most cases, there is increasing interest in the role of genetic factors. Indeed, the role of inheritable variations in predisposing patients to ADRs has been appreciated since the late 1950s and early 1960s through the discovery of deficiencies in enzymes such as pseudocholinesterase (butyrylcholinesterase) and glucose-6-phosphate dehydrogenase (G6PD). More recently, with the first draft of the human genome just completed, there has been renewed interest in this area with the introduction of terms such as pharmacogenomics and toxicogenomics. Essentially, the aim of pharmacogenomics and pharmacogenetics is to produce personalized medicines, whereby administration of the drug class and dosage is tailored to an individual genotype. Thus, the term pharmacogenetics embraces both efficacy and toxicity.

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The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") specifically inhibit the enzyme HMG-CoA reductase which catalyzes the rate limiting step in cholesterol biosynthesis. These drugs are effective in reducing the primary and secondary risk of coronary artery disease and coronary events, such

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as heart attack, in middle-aged and older men and women, in both diabetic and nondiabetic patients, and are often prescribed for patients with hyperlipidemia. Statins used in secondary prevention of coronary artery or heart disease significantly reduce the risk of stroke, total mortality and morbidity and attacks of myocardial ischemia; the use of statins is also associated with improvements in endothelial and fibrinolytic functions and decreased platelet thrombus formation.

The tolerability of these drugs during long term administration is an important issue. Adverse reactions involving skeletal muscle are not uncommon, and sometimes serious adverse reactions involving skeletal muscle such as myopathy and rhabdomyolysis may occur, requiring discontinuation of the drug. In addition an increase in serum creatine kinase (CK) may be a sign of a statin related adverse event. The extend of such adverse events can be read from the extend of the CK level increase (as compared to the upper limit of normal [ULN]).

Occasionally arthralgia, alone or in association with myalgia, has been reported. Also an elevation of liver transaminases has been associated with statin administration.

It was shown that the drug response to statin therapy is a class effects, i.e. all known and presumably also all so far undiscovered statins share the same benefical and harmful effects (Ucar, M. et al., Drug Safety 2000, 22:441). It follows that the discovery of diagnostic tools to predict the drug response to a single statin will also be of aid to guide therapy with other statins.

The present invention provides diagnostic tests to predict the patient's individual 25 response to statin therapy. Such responses include, but are not limited by the extent of adverse drug reactions, the level of lipid lowering or the drug's influence on disease states. Those diagnostic tests may predict the response to statin therapy either alone or in combination with another diagnostic test or another drug regimen. 30

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## Detailed Description of the Invention

The present invention is based at least in part on the discovery that a specific allele of a polymorphic region of a so called "candidate gene" (as defined below) is associated with CVD or drug response.

For the present invention the following candidate genes were analyzed:

- Genes found to be expressed in cardiac tissue (Hwang et al., Circulation 1997, 96:4146-4203).
- Genes from the following metabolic pathways and their regulatory elements:

#### Lipid metabolism

Numerous studies have shown a connection between serum lipid levels and cardiovascular diseases. Candidate genes falling into this group include but are not limited by genes of the cholesterol pathway, apolipoproteins and their modifiying factors.

#### 20 Coagulation

Ischemic diseases of the heart and in particular myocardial infarction may be caused by a thrombotic occlusion. Genes falling into this group include all genes of the coagulation cascade and their regulatory elements.

#### Inflammation

Complications of atherosclerosis are the most common causes of death in Western societies. In broad outline atherosclerosis can be considered to be a form of chronic inflammation resulting from interaction modified lipoproteins, monocyte-derived macrophages, T cells, and the normal cellular elements of the arterial wall. This

inflammatory process can ultimately lead to the development of complex lesions, or plaques, that protrude into the arterial lumen. Finally plaque rupture and thrombosis result in the acute clinical complications of myocardial infarction and stroke (Glass et al., Cell 2001, 104:503-516).

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It follows that all genes related to inflammatory processes, including but not limited by cytokines, cytokine receptors and cell adhesion molecules are candidate genes for CVD.

## 10 Glucose and energy metabolism

As glucose and energy metabolism is interdependent with the metabolism of lipids (see above) also the former pathways contain candidate genes. Energy metabolism in general also relates to obesity, which is an independent risk factor for CVD (Melanson et al., Cardiol Rev 2001 9:202-207). In addition high blood glucose levels are associated with many microvascular and macrovascular complications and may therefore affect an individuals disposition to CVD (Duckworth, Curr Atheroscler Rep 2001, 3:383-391).

## 20 Hypertension

As hypertension is an independent risk factor for CVD, also genes that are involved in the regulation of systolic and diastolic blood pressure affect an individuals risk for CVD (Safar, Curr Opin Cardiol 2000, 15:258-263). Interestingly hypertension and diabetes (see above) appear to be interdependent, since hypertension is approximately twice as frequent in patients with diabetes compared with patients without the disease. Conversely, recent data suggest that hypertensive persons are more predisposed to the development of diabetes than are normotensive persons (Sowers et al., Hypertension 2001, 37:1053-1059).

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### Genes related to drug response

Those genes include metabolic pathways involved in the absorption, distribution, metabolism, excretion and toxicity (ADMET) of drugs. Prominent members of this group are the cytochrome P450 proteins which catalyze many reactions involved in drug metabolism.

#### Unclassified genes

As stated above, the mechanisms that lead to cardiovascular diseases or define the patient's individual response to drugs are not completely elucidated. Hence also candidate genes were analysed, which could not be assigned to the above listed categories. The present invention is based at least in part on the discovery of polymorphisms, that lie in genomic regions of unknown physiological function.

Results

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After conducting an association study, we surprisingly found polymorphic sites in a number of candidate genes which show a strong correlation with the following phenotypes of the patients analysed: "Healthy" as used herein refers to individuals that neither suffer from existing CVD, nor exhibit an increased risk for CVD through their serum lipid level profile. "CVD prone" as used herein refers to individuals with existing CVD and/or a serum lipid profile that confers a high risk to get CVD (see Table 1a for definitions of healthy and CVD prone serum lipid levels). "High responder" as used herein refers to patients who benefit from relatively small amounts of a given drug. "Low responder" as used herein refers to patients who need relatively high doses in order to obtain benefit from the medication. "Tolerant patient" refers to individuals who can tolerate high doses of a medicament without exhibiting adverse drug reactions. "ADR patient" as used herein refers to individuals who suffer from ADR or show clinical symptoms (like creatine kinase elevation in

blood) even after receiving only minor doses of a medicament (see Table 1b for a detailed definition of drug response phenotypes).

Polymorphic sites in candidate genes that were found to be significantly associated with either of the above mentioned phenotypes will be referred to as "phenotype associated SNPs" (PA SNPs). The respective genomic loci that harbour PA SNPs will be referred to as "phenotype associated genes" (PA genes), irrespective of the actual function of this gene locus.

As PA SNPs are linked to other SNPs in neighboring genes on a chromosome (Linkage Disequilibrium) those SNPs could also be used as marker SNPs. In a recent publication it was shown that SNPs are linked over 100 kb in some cases more than 150 kb (Reich D.E. et al. Nature 411, 199-204, 2001). Hence SNPs lying in regions neighbouring PA SNPs could be linked to the latter and by this being a diagnostic marker. These associations could be performed as described for the gene polymorphism in methods.

### **Definitions**

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For convenience, the meaning of certain terms and phrases employed in the specification, examples, and appended claims are provided below. Moreover, the definitions by itself are intended to explain a further background of the invention.

The term "allele", which is used interchangeably herein with "allelic variant" refers to alternative forms of a gene or portions thereof. Alleles occupy the same locus or position on homologous chromosomes. When a subject has two identical alleles of a gene, the subject is said to be homozygous for the gene or allele. When a subject has two different alleles of a gene, the subject is said to be heterozygous for the gene. Alleles of a specific gene can differ from each other in a single nucleotide, or several—nucleotides, and ean-include substitutions, deletions, and insertions of nucleotides. An allele of a gene can also be a form of a gene containing a mutation.

The term "allelic variant of a polymorphic region of a gene" refers to a region of a gene having one of several nucleotide sequences found in that region of the gene in other individuals.

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"Homology" or "identity" or "similarity" refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. An "unrelated" or "non-homologous" sequence shares less than 40% identity, though preferably less than 25% identity, with one of the sequences of the present invention.

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The term "a homologue of a nucleic acid" refers to a nucleic acid having a nucleotide sequence having a certain degree of homology with the nucleotide sequence of the nucleic acid or complement thereof. A homologue of a double stranded nucleic acid having SEQ ID NO. X is intended to include nucleic acids having a nucleotide sequence which has a certain degree of homology with SEQ ID NO. X or with the complement thereof. Preferred homologous of nucleic acids are capable of hybridizing to the nucleic acid or complement thereof.

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The term "interact" as used herein is meant to include detectable interactions between molecules, such as can be detected using, for example, a hybridization assay.

Lerm interact is also meant to include "binding" interactions between molecules. Interactions may be, for example, protein-protein, protein-nucleic acid, protein-small molecule or small molecule-nucleic acid in nature.

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The term "intronic sequence" or "intronic nucleotide sequence" refers to the nucleotide sequence of an intron or portion thereof.

The term "isolated" as used herein with respect to nucleic acids, such as DNA or RNA, refers to molecules separated from other DNAs or RNAs, respectively, that are present in the natural source of the macromolecule. The term isolated as used herein also refers to a nucleic acid or peptide that is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized.

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Moreover, an "isolated nucleic acid" is meant to include nucleic acid fragments which are not naturally occurring as fragments and would not be found in the natural state. The term "isolated" is also used herein to refer to polypeptides which are isolated from other cellular proteins and is meant to encompass both purified and recombinant polypeptides.

The term "lipid" shall refer to a fat or fat-like substance that is insoluble in polar solvents such as water. The term "lipid" is intended to include true fats (e.g. esters of fatty acids and glycerol); lipids (phospholipids, cerebrosides, waxes); sterols (cholesterol, ergosterol) and lipoproteins (e.g. HDL, LDL and VLDL).

The term "locus" refers to a specific position in a chromosome. For example, a locus of a gene refers to the chromosomal position of the gene.

- The term "modulation" as used herein refers to both up-regulation, (i.e., activation or stimulation), for example by agonizing, and down-regulation (i.e. inhibition or suppression), for example by antagonizing of a bioactivity (e.g. expression of a gene).
- The term "molecular-structure" of a gene or a portion thereof refers to the structure as defined by the nucleotide content (including deletions, substitutions, additions of one

or more nucleotides), the nucleotide sequence, the state of methylation, and/or any other modification of the gene or portion thereof.

The term "mutated gene" refers to an allelic form of a gene, which is capable of altering the phenotype of a subject having the mutated gene relative to a subject which does not have the mutated gene. If a subject must be homozygous for this mutation to have an altered phenotype, the mutation is said to be recessive. If one copy of the mutated gene is sufficient to alter the genotype of the subject, the mutation is said to be dominant. If a subject has one copy of the mutated gene and has a phenotype that is intermediate between that of a homozygous and that of a heterozygous (for that gene) subject, the mutation is said to be co-dominant.

As used herein, the term "nucleic acid" refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include, as equivalents, derivatives, variants and analogs of either RNA or DNA made from nucleotide analogs, including peptide nucleic acids (PNA), morpholino oligonucleotides (J. Summerton and D. Weller, Antisense and Nucleic Acid Drug Development 7:187 (1997)) and, as applicable to the embodiment being described, single (sense or antisense) and double-stranded polynucleotides. Deoxyribonucleotides include deoxyadenosine, deoxycytidine, deoxyguanosine, and deoxythymidine. For purposes of clarity, when referring herein to a nucleotide of a nucleic acid, which can be DNA or an RNA, the term "adenosine", "cytidine", "guanosine", and "thymidine" are used. It is understood that if the nucleic acid is RNA, a nucleotide having a uracil base is uridine.

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The term "nucleotide sequence complementary to the nucleotide sequence set forth in SEQ ID NO. x" refers to the nucleotide sequence of the complementary strand of a nucleic acid strand having SEQ ID NO. x. The term "complementary strand" is used herein interchangeably with the term "complement". The complement of a nucleic acid strand can be the complement of a coding strand or the complement of a non-coding strand. When referring to double stranded nucleic acids, the complement of a

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nucleic acid having SEQ ID NO. x refers to the complementary strand of the strand having SEQ ID NO. x or to any nucleic acid having the nucleotide sequence of the complementary strand of SEQ ID NO. x. When referring to a single stranded nucleic acid having the nucleotide sequence SEQ ID NO. x, the complement of this nucleic acid is a nucleic acid having a nucleotide sequence which is complementary to that of SEQ ID NO. x. The nucleotide sequences and complementary sequences thereof are always given in the 5' to 3' direction. The term "complement" and "reverse complement" are used interchangeably herein.

The term "operably linked" is intended to mean that the promoter is associated with the nucleic acid in such a manner as to facilitate transcription of the nucleic acid.

The term "polymorphism" refers to the coexistence of more than one form of a gene or portion thereof. A portion of a gene of which there are at least two different forms, i.e., two different nucleotide sequences, is referred to as a "polymorphic region of a gene". A polymorphic region can be a single nucleotide, the identity of which differs in different alleles. A polymorphic region can also be several nucleotides long.

A "polymorphic gene" refers to a gene having at least one polymorphic region.

To describe a "polymorphic site" in a nucleotide sequence often there is used an "ambiguity code" that stands for the possible variations of nucleotides in one site. The list of ambiguity codes is summarized in the following table:

Codes	
(IUPAC Nomenclature)	
c/g/t	
. a/g/t	
a/c/t	
g/t	
a/c	
· a/c/g/t	
a/g	
c/g	
a/c/g	
a/t	
c/t	

So, for example, a "R" in a nucleotide sequence means that either an "a" or a "g" could be at that position.

The terms "protein", "polypeptide" and "peptide" are used interchangeably herein when referring to a gene product.

A "regulatory element", also termed herein "regulatory sequence is intended to include elements which are capable of modulating transcription from a basic promoter and include elements such as enhancers and silencers. The term "enhancer", also referred to herein as "enhancer element", is intended to include regulatory elements capable of increasing, stimulating, or enhancing transcription from a basic promoter. The term "silencer", also referred to herein as "silencer element" is intended to include regulatory elements capable of decreasing, inhibiting, or repressing transcription from a basic promoter. Regulatory elements are typically present in 5' flanking regions of genes. However, regulatory elements have also been shown to be present in other regions of a gene, in particular in introns. Thus, it is possible that genes have regulatory elements located in introns, exons, coding

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regions, and 3' flanking sequences. Such regulatory elements are also intended to be encompassed by the present invention and can be identified by any of the assays that can be used to identify regulatory elements in 5' flanking regions of genes.

The term "regulatory element" further encompasses "tissue specific" regulatory elements, i.e., regulatory elements which effect expression of the selected DNA sequence preferentially in specific cells (e.g., cells of a specific tissue). gene expression occurs preferentially in a specific cell if expression in this cell type is significantly higher than expression in other cell types. The term "regulatory element" also encompasses non-tissue specific regulatory elements, i.e., regulatory elements which are active in most cell types. Furthermore, a regulatory element can be a constitutive regulatory element, i.e., a regulatory element which constitutively regulates transcription, as opposed to a regulatory element which is inducible, i.e., a regulatory element which is active primarily in response to a stimulus. A stimulus can be, e.g., a molecule, such as a hormone, cytokine, heavy metal, phorbol ester, cyclic AMP (cAMP), or retinoic acid.

Regulatory elements are typically bound by proteins, e.g., transcription factors. The term "transcription factor" is intended to include proteins or modified forms thereof, which interact preferentially with specific nucleic acid sequences, i.e., regulatory elements, and which in appropriate conditions stimulate or repress transcription. Some transcription factors are active when they are in the form of a monomer. Alternatively, other transcription factors are active in the form of a dimer consisting of two identical proteins or different proteins (heterodimer). Modified forms of transcription factors are intended to refer to transcription factors having a post-translational modification, such as the attachment of a phosphate group. The activity of a transcription factor is frequently modulated by a post-translational modification. For example, certain transcription factors are active only if they are phosphorylated on specific residues. Alternatively, transcription factors can be active in the absence of phosphorylated residues and become inactivated by phosphorylation. A list of

known transcription factors and their DNA binding site can be found, e.g., in public databases, e.g., TFMATRIX Transcription Factor Binding Site Profile database.

As used herein, the term "specifically hybridizes" or "specifically detects" refers to the ability of a nucleic acid molecule of the invention to hybridize to at least approximately 6, 12, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130 or 140 consecutive nucleotides of either strand of a gene.

The term "wild-type allele" refers to an allele of a gene which, when present in two copies in a subject results in a wild-type phenotype. There can be several different wild-type alleles of a specific gene, since certain nucleotide changes in a gene may not affect the phenotype of a subject having two copies of the gene with the nucleotide changes.

"Adverse drug reaction" (ADR) as used herein refers to an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, whichpredicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product. In it's most severe form an ADR might lead to the death of an individual.

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The term "Drug Response" is intended to mean any response that a patient exhibits upon drug administration. Specifically drug response includes beneficial, i.e. desired drug effects, ADR or no detectable reaction at all. More specifically the term drug response could also have a qualitative meaning, i.e. it embraces low or high beneficial effects, respectively and mild or severe ADR, respectively. The term "Statin Response" as used herein refers to drug response after statin administration. An individual drug response includes also a good or bad metabolizing of the drug, meaning that "bad metabolizers" accumulate the drug in the body and by this could show side effects of the drug due to accumulative overdoses.

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"Candidate gene" as used herein includes genes that can be assigned to either normal cardiovascular function or to metabolic pathways that are related to onset and/or progression of cardiovascular diseases.

- With regard to drug response the term "candidate gene" includes genes that can be assigned to distinct phenotypes regarding the patient's response to drug administration. Those phenotypes may include patients who benefit from relatively small amounts of a given drug (high responders) or patients who need relatively high doses in order to obtain the same benefit (low responders). In addition those phenotypes may include patients who can tolerate high doses of a medicament without exhibiting ADR, or patients who suffer from ADR even after receiving only low doses of a medicament.
- As neither the development of cardiovascular diseases nor the patient's response to drug administration is completely understood, the term "candidate gene" may also comprise genes with presently unknown function.
  - "PA SNP" (phenotype associated SNP) refers to a polymorphic site which shows a significant association with a patients phenotype (healthy, diseased, low or high responder, drug tolerant, ADR prone, etc.)
    - "PA gene" (phenotype associated gene) refers to a genomic locus harbouring a PA SNP, irrespective of the actual function of this gene locus.
- 25 PA gene polypeptide refers to a polypeptide encoded at least in part by a PA gene.
  - The term "Secondary SNP" is intended to mean a SNP that is in neighborhood to at least one other ("primary") SNP. Due to linkage disequillibrium both primary and secondary SNP(s) might shown a similar association with a phenotype.

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The term "Haplotype" as used herein refers to a group of two or more SNPs that are functionally and/or spatially linked. I.e. haplotypes define groups of SNPs that lie inside genes belonging to identical (or related metabolic) pathways and/or lie on the same chromosome. Haplotypes are expected to give better predictive/diagnostic information than a single SNP

The term "statin" is intended to embrace all inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Statins specifically inhibit the enzyme HMG-CoA reductase which catalyzes the rate limiting step in cholesterol biosynthesis. Known statins are Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Pravastatin and Simyastatin.

## Methods for Assessing Cardiovascular Status

The present invention provides diagnostic methods for assessing cardiovascular status in a human individual. Cardiovascular status as used herein refers to the physiological status of an individual's cardiovascular system as reflected in one or more markers or indicators. Status markers include without limitation clinical measurements such as, e.g., blood pressure, electrocardiographic profile, and differentiated blood flow analysis as well as measurements of LDL- and HDL-Cholesterol levels, other lipids and other well established clinical parameters that are standard in the art. Status markers according to the invention include diagnoses of one or more cardiovascular syndromes, such as, e.g., hypertension, acute myocardial infarction, silent myocardial infarction, stroke, and atherosclerosis. It will be understood that a diagnosis of a cardiovascular syndrome made by a medical practitioner encompasses clinical measurements and medical judgement. Status markers according to the invention are assessed using conventional methods well known in the art. Also included in the evaluation of cardiovascular status are quantitative or qualitative changes in status markers with time, such as would be used, e.g., in the determination of an individual's response to a particular therapeutic regimen.

The methods are carried out by the steps of:

- (i) determining the sequence of one or more polymorphic positions within one, several or all of the genes listed in Examples or other genes mentioned in this file in the individual to establish a polymorphic pattern for the individual; and
- comparing the polymorphic pattern established in (i) with the polymorphic (ii) patterns of humans exhibiting different markers of cardiovascular status. The 10 polymorphic pattern of the individual is, preferably, highly similar and, most preferably, identical to the polymorphic pattern of individuals who exhibit particular status markers, cardiovascular syndromes, and/or particular patterns of response to therapeutic interventions. Polymorphic patterns may also include polymorphic positions in other genes which are shown, in combination with one or more polymorphic positions in the genes listed in the 15 Examples, to correlate with the presence of particular status markers. In one embodiment, the method involves comparing an individual's polymorphic pattern with polymorphic patterns of individuals who have been shown to respond positively or negatively to a particular therapeutic regimen. 20 Therapeutic regimen as used herein refers to treatments aimed at the elimination or amelioration of symptoms and events associated cardiovascular disease. Such treatments include without limitation one or more of alteration in diet, lifestyle, and exercise regimen; invasive and noninvasive surgical techniques such as atherectomy, angioplasty, and coronary bypass surgery; 25 and pharmaceutical interventions, such as administration of ACE inhibitors, angiotensin II receptor antagonists, diuretics, alpha-adrenoreceptor antagonists, cardiac glycosides, phosphodiesterase inhibitors, beta-adrenoreceptor antagonists, calcium channel blockers, HMG-CoA reductase inhibitors, imidazoline receptor blockers, endothelin receptor blockers, organic nitrites, 30 and modulators of protein function of genes listed in the Examples. Interventions with pharmaceutical agents not yet known whose activity

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correlates with particular polymorphic patterns associated with cardiovascular disease are also encompassed. It is contemplated, for example, that patients who are candidates for a particular therapeutic regimen will be screened for polymorphic patterns that correlate with responsivity to that particular regimen.

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In a preferred embodiment, the method involves comparing an individual's polymorphic pattern with polymorphic patterns of individuals who exhibit or have exhibited one or more markers of cardiovascular disease, such as, e.g., elevated LDL-Cholesterol levels, high blood pressure, abnormal electrocardiographic profile, myocardial infarction, stroke, or atherosclerosis.

In another embodiment, the method involves comparing an individual's polymorphic pattern with polymorphic patterns of individuals who exhibit or have exhibited one or more drug related phenotypes, such as, e.g., low or high drug response, or adverse drug reactions.

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In practicing the methods of the invention, an individual's polymorphic pattern can be established by obtaining DNA from the individual and determining the sequence at predetermined polymorphic positions in the genes such as those described in this file.

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The DNA may be obtained from any cell source. Non-limiting examples of cell sources available in clinical practice include blood cells, buccal cells, cervicovaginal cells, epithelial cells from urine, fetal cells, or any cells present in tissue obtained by biopsy. Cells may also be obtained from body fluids, including without limitation blood, saliva, sweat, urine, cerebrospinal fluid, feces, and tissue exudates at the site of infection or inflammation. DNA is extracted from the cell source or body fluid using any of the numerous methods that are standard in the art. It will be understood that the particular method used to extract DNA will depend on the nature of the source.

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## Diagnostic and Prognostic Assays

The present invention provides methods for determining the molecular structure of at least one polymorphic region of a gene, specific allelic variants of said polymorphic region being associated with cardiovascular disease. In one embodiment, determining the molecular structure of a polymorphic region of a gene comprises determining the identity of the allelic variant. A polymorphic region of a gene, of which specific alleles are associated with cardiovascular disease can be located in an exon, an intron, at an intron/exon border, or in the promoter of the gene.

The invention provides methods for determining whether a subject has, or is at risk, of developing a cardiovascular disease. Such disorders can be associated with an aberrant gene activity, e.g., abnormal binding to a form of a lipid, or an aberrant gene protein level. An aberrant gene protein level can result from an aberrant transcription or post-transcriptional regulation. Thus, allelic differences in specific regions of a gene can result in differences of gene protein due to differences in regulation of expression. In particular, some of the identified polymorphisms in the human gene may be associated with differences in the level of transcription, RNA maturation, splicing, or translation of the gene or transcription product.

In preferred embodiments, the methods of the invention can be characterized as comprising detecting, in a sample of cells from the subject, the presence or absence of a specific allelic variant of one or more polymorphic regions of a gene. The allelic differences can be: (i) a difference in the identity of at least one nucleotide or (ii) a difference in the number of nucleotides, which difference can be a single nucleotide or several nucleotides.

A preferred detection method is allele specific hybridization using probes overlapping the polymorphic-site-and-having-about-5, 10, 20, 25, or 30 nucleotides around the polymorphic region. Examples of probes for detecting specific allelic

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variants of the polymorphic region located in intron X are probes comprising a nucleotide sequence set forth in any of SEQ ID NO. X. In a preferred embodiment of the invention, several probes capable of hybridizing specifically to allelic variants are attached to a solid phase support, e.g., a "chip". Oligonucleotides can be bound to a solid support by a variety of processes, including lithography. For example a chip can hold up to 250,000 oligonucleotides (GeneChip, Affymetrix). Mutation detection analysis using these chips comprising oligonucleotides, also termed "DNA probe arrays" is described e.g., in Cronin et al. (1996) Human Mutation 7:244 and in Kozal et al. (1996) Nature Medicine 2:753. In one embodiment, a chip comprises all the allelic variants of at least one polymorphic region of a gene. The solid phase support is then contacted with a test nucleic acid and hybridization to the specific probes is detected. Accordingly, the identity of numerous allelic variants of one or more genes can be identified in a simple hybridization experiment. For example, the identity of the allelic variant of the nucleotide polymorphism of nucleotide A or G at position 33 of Seq ID 1 (baySNP179) and that of other possible polymorphic regions can be determined in a single hybridization experiment.

In other detection methods, it is necessary to first amplify at least a portion of a gene prior to identifying the allelic variant. Amplification can be performed, e.g., by PCR and/or LCR, according to methods known in the art. In one embodiment, genomic DNA of a cell is exposed to two PCR primers and amplification for a number of cycles sufficient to produce the required amount of amplified DNA. In preferred embodiments, the primers are located between 40 and 350 base pairs apart. Preferred primers for amplifying gene fragments of genes of this file are listed in Table 2 in the Examples.

(Guatelli, J. C. et al., 1990, Proc. Natl. Acad. Sci. U.S.A. 87:1874-1878), transcriptional amplification system (Kwoh, D. Y. et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:1173-1177), Q-Beta Replicase (Lizardi, P. M. et al., 1988, Bio/Technology 6:1197), or any other nucleic acid amplification method, followed

by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In one embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence at least a portion of a gene and detect allelic variants, e.g., mutations, by comparing the sequence of the sample sequence with the corresponding wild-type (control) sequence. Exemplary sequencing reactions include those based on techniques developed by Maxam and Gilbert (Proc. Natl Acad Sci. USA (1977) 74:560) or Sanger (Sanger et al (1977) Proc. Nat. Acad. Sci 74:5463). It is also contemplated that any of a variety of automated sequencing procedures may be utilized when performing the subject assays (Biotechniques (1995) 19:448), including sequencing by mass spectrometry (see, for example, U.S. Pat. No. 5,547,835 and international patent application Publication Number WO 94/16101, entitled DNA Sequencing by Mass Spectrometry by H. Koster; U.S. Pat. No. 5,547,835 and international patent application Publication Number WO 94/21822 entitled "DNA Sequencing by Mass Spectrometry Via Exonuclease Degradation" by H. Koster), and U.S. Pat. No. 5,605,798 and International Patent Application No. PCT/US96/03651 entitled DNA Diagnostics Based on Mass Spectrometry by H. Koster; Cohen et al. (1996) Adv Chromatogr 36:127-162; and Griffin et al. (1993) Appl Biochem Biotechnol 38:147-159). It will be evident to one skilled in the art that, for certain embodiments, the occurrence of only one, two or three of the nucleic acid bases need be determined in the sequencing reaction. For instance, A-track or the like, e.g., where only one nucleotide is detected, can be carried out.

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Yet other sequencing methods are disclosed, e.g., in U.S. Pat. No. 5,580,732 entitled "Method of DNA sequencing employing a mixed DNA-polymer chain probe" and U.S. Pat. No. 5,571,676 entitled "Method for mismatch-directed in vitro DNA sequencing".

In some cases, the presence of a specific allele of a gene in DNA from a subject can be shown by restriction enzyme analysis. For example, a specific nucleotide polymorphism can result in a nucleotide sequence comprising a restriction site which is absent from the nucleotide sequence of another allelic variant.

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In other embodiments, alterations in electrophoretic mobility is used to identify the type of gene allelic variant. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita et al. (1989) Proc Natl. Acad. Sci USA 86:2766, see also Cotton (1993) Mutat Res 285:125-144; and Hayashi (1992) Genet Anal Tech Appl 9:73-79). Single-stranded DNA fragments of sample and control nucleic acids are denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In another preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen et al. (1991) Trends Genet 7:5).

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In yet another embodiment, the identity of an allelic variant of a polymorphic region is obtained by analyzing the movement of a nucleic acid comprising the polymorphic region in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers et al (1985) Nature 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing agent gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) Biophys Chem 265:1275).

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Examples of techniques for detecting differences of at least one nucleotide between 2 nucleic acids include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide probes may be prepared in which the known polymorphic nucleotide is placed centrally (allele-specific probes) and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki et al. (1986) Nature 324:163); Saiki et al (1989) Proc. Natl Acad. Sci USA 86:6230; and Wallace et al. (1979) Nucl. Acids Res. 6:3543). Such allele specific oligonucleotide hybridization techniques may be used for the simultaneous detection of several nucleotide changes in different polymorphic regions of gene. For example, oligonucleotides having nucleotide sequences of specific allelic variants are attached to a hybridizing membrane and this membrane is then hybridized with labeled sample nucleic acid. Analysis of the hybridization signal will then reveal the identity of the nucleotides of the sample nucleic acid.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used. Oligonucleotides used as primers for specific amplification may carry the allelic variant of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs et al (1989) Nucleic Acids Res. 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) Tibtech 11:238; Newton et al. (1989) Nucl. Acids Res. 17:2503). This technique is also termed "PROBE" for Probe Oligo Base Extension. In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini et al (1992) Mol. Cell Probes 6:1).

In another embodiment, identification of the allelic variant is carried out using an oligonucleotide ligation assay (OLA), as described, e.g., in U.S. Pat. No. 4,998,617 and in Landegren, U. et al., Science-241:1077-1080-(1988). The OLA protocol uses two oligonucleotides which are designed to be capable of hybridizing to abutting

sequences of a single strand of a target. One of the oligonucleotides is linked to a separation marker, e.g., biotinylated, and the other is detectably labeled. If the precise complementary sequence is found in a target molecule, the oligonucleotides will hybridize such that their termini abut, and create a ligation substrate. Ligation then permits the labeled oligonucleotide to be recovered using avidin, or another biotin ligand. Nickerson, D. A. et al. have described a nucleic acid detection assay that combines attributes of PCR and OLA (Nickerson, D. A. et al., Proc. Natl. Acad. Sci. (U.S.A.) 87:8923-8927 (1990). In this method, PCR is used to achieve the exponential amplification of target DNA, which is then detected using OLA.

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Several techniques based on this OLA method have been developed and can be used to detect specific allelic variants of a polymorphic region of a gene. For example, U.S. Pat. No. 5,593,826 discloses an OLA using an oligonucleotide having 3'-amino group and a 5'-phosphorylated oligonucleotide to form a conjugate having a phosphoramidate linkage. In another variation of OLA described in Tobe et al. ((1996)Nucleic Acids Res 24: 3728), OLA combined with PCR permits typing of two alleles in a single microtiter well. By marking each of the allele-specific primers with a unique hapten, i.e. digoxigenin and fluorescein, each LA reaction can be detected by using hapten specific antibodies that are labeled with different enzyme reporters, alkaline phosphatase or horseradish peroxidase. This system permits the detection of the two alleles using a high throughput format that leads to the production of two different colors.

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The invention further provides methods for detecting single nucleotide polymorphisms in a gene. Because single nucleotide polymorphisms constitute sites of variation flanked by regions of invariant sequence, their analysis requires no more than the determination of the identity of the single nucleotide present at the site of variation and it is unnecessary to determine a complete gene sequence for each patient. Several methods have been developed to facilitate the analysis of such single nucleotide polymorphisms.

In one embodiment, the single base polymorphism can be detected by using a specialized exonuclease-resistant nucleotide, as disclosed, e.g., in Mundy, C. R. (U.S. Pat. No. 4,656,127). According to the method, a primer complementary to the allelic sequence immediately 3' to the polymorphic site is permitted to hybridize to a target molecule obtained from a particular animal or human. If the polymorphic site on the target molecule contains a nucleotide that is complementary to the particular exonuclease-resistant nucleotide derivative present, then that derivative will be incorporated onto the end of the hybridized primer. Such incorporation renders the primer resistant to exonuclease, and thereby permits its detection. Since the identity of the exonuclease-resistant derivative of the sample is known, a finding that the primer has become resistant to exonucleases reveals that the nucleotide present in the polymorphic site of the target molecule was complementary to that of the nucleotide derivative used in the reaction. This method has the advantage that it does not require the determination of large amounts of extraneous sequence data.

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In another embodiment of the invention, a solution-based method is used for determining the identity of the nucleotide of a polymorphic site. Cohen, D. et al. (French Patent 2,650,840; PCT Appln. No. WO91/02087). As in the Mundy method of U.S. Pat. No. 4,656,127, a primer is employed that is complementary to allelic sequences immediately 3' to a polymorphic site. The method determines the identity of the nucleotide of that site using labeled dideoxynucleotide derivatives, which, if complementary to the nucleotide of the polymorphic site will become incorporated onto the terminus of the primer.

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An alternative method, known as Genetic Bit Analysis or GBA TM is described by Goelet, P. et al. (PCT Appln. No. 92/15712). The method of Goelet, P. et al. uses mixtures of labeled terminators and a primer that is complementary to the sequence 3' to a polymorphic site. The labeled terminator that is incorporated is thus determined by, and complementary to, the nucleotide present in the polymorphic site of-the-target molecule being evaluated. In contrast to the method of Cohen et al. (French Patent 2,650,840; PCT Appln. No. WO91/02087) the method of Goelet, P. et

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al. is preferably a heterogeneous phase assay, in which the primer or the target molecule is immobilized to a solid phase.

Recently, several primer-guided nucleotide incorporation procedures for assaying polymorphic sites in DNA have been described (Komher, J. S. et al., Nucl. Acids. Res. 17:7779-7784 (1989); Sokolov, B. P., Nucl. Acids Res. 18:3671 (1990); Syvanen, A. -C., et al., Genomics 8:684-692 (1990), Kuppuswamy, M. N. et al., Proc. Natl. Acad. Sci. (U.S.A.) 88:1143-1147 (1991); Prezant, T. R. et al., Hum. Mutat. 1:159-164 (1992); Ugozzoli, L. et al., GATA 9:107-112 (1992); Nyren, P. et al., Anal. Biochem. 208:171-175 (1993)). These methods differ from GBA TM in that they all rely on the incorporation of labeled deoxynucleotides to discriminate between bases at a polymorphic site. In such a format, since the signal is proportional to the number of deoxynucleotides incorporated, polymorphisms that occur in runs of the same nucleotide can result in signals that are proportional to the length of the run (Syvanen, A.-C., et al., Amer. J. Hum. Genet. 52:46-59 (1993)).

For determining the identity of the allelic variant of a polymorphic region located in the coding region of a gene, yet other methods than those described above can be used. For example, identification of an allelic variant which encodes a mutated gene protein can be performed by using an antibody specifically recognizing the mutant protein in, e.g., immunohistochemistry or immunoprecipitation. Antibodies to wild-type gene protein are described, e.g., in Acton et al. (1999) Science 271:518 (antimouse gene antibody cross-reactive with human gene). Other antibodies to wild-type gene or mutated forms of gene proteins can be prepared according to methods known in the art. Alternatively, one can also measure an activity of an gene protein, such as binding to a lipid or lipoprotein. Binding assays are known in the art and involve, s.g., obtaining cells from a subject, and performing binding experiments with a labeled lipid, to determine whether binding to the mutated form of the receptor differs from binding to the wild-type of the receptor.

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If a polymorphic region is located in an exon, either in a coding or non-coding region of the gene, the identity of the allelic variant can be determined by determining the molecular structure of the mRNA, pre-mRNA, or cDNA. The molecular structure can be determined using any of the above described methods for determining the molecular structure of the genomic DNA, e.g., sequencing and SSCP.

The methods described herein may be performed, for example, by utilizing prepackaged diagnostic kits, such as those described above, comprising at least one probe or primer nucleic acid described herein, which may be conveniently used, e.g., to determine whether a subject has or is at risk of developing a disease associated with a specific gene allelic variant.

Sample nucleic acid for using in the above-described diagnostic and prognostic methods can be obtained from any cell type or tissue of a subject. For example, a subject's bodily fluid (e.g. blood) can be obtained by known techniques (e.g. venipuncture) or from human tissues like heart (biopsies, transplanted organs). Alternatively, nucleic acid tests can be performed on dry samples (e.g. hair or skin). Fetal nucleic acid samples for prenatal diagnostics can be obtained from maternal blood as described in International Patent Application No.WO91/07660 to Bianchi. Alternatively, amniocytes or chorionic villi may be obtained for performing prenatal testing.

Diagnostic procedures may also be performed in situ directly upon tissue sections (fixed and/or frozen) of patient tissue obtained from biopsies or resections, such that no nucleic acid purification is necessary. Nucleic acid reagents may be used as probes and/or primers for such in situ procedures (see, for example, Nuovo, G. J., 1992, PCR in situ hybridization: protocols and applications, Raven Press, New York).

In addition to methods which focus primarily on the detection of one nucleic acidsequence, profiles may also be assessed in such detection schemes. Fingerprint profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR.

In practicing the present invention, the distribution of polymorphic patterns in a large number of individuals exhibiting particular markers of cardiovascular status or drug response is determined by any of the methods described above, and compared with the distribution of polymorphic patterns in patients that have been matched for age, ethnic origin, and/or any other statistically or medically relevant parameters, who exhibit quantitatively or qualitatively different status markers. Correlations are achieved using any method known in the art, including nominal logistic regression, chi square tests or standard least squares regression analysis. In this manner, it is possible to establish statistically significant correlations between particular polymorphic patterns and particular cardiovascular statuses (given in p values). It is further possible to establish statistically significant correlations between particular polymorphic patterns and changes in cardiovascular status or drug response such as, would result, e.g., from particular treatment regimens. In this manner, it is possible to correlate polymorphic patterns with responsivity to particular treatments.

In another embodiment of the present invention two or more polymorphic regions are combined to define so called 'haplotypes'. Haplotypes are groups of two or more SNPs that are functionally and/or spatially linked. It is possible to combine SNPs that are disclosed in the present invention either with each other or with additional polymorphic regions to form a haplotype. Haplotypes are expected to give better predictive/diagnostic information than a single SNP.

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In a preferred embodiment of the present invention a panel of SNPs/haplotypes is defined that predicts the risk for CVD or drug response. This predictive panel is then used for genotyping of patients on a platform that can genotype multiple SNPs at the same time (Multiplexing). Preferred platforms are e.g. gene chips (Affymetrix) or the Luminex LabMAP reader. The subsequent identification and evaluation of a patient's haplotype can then help to guide specific and individualized therapy.

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For example the present invention can identify patients exhibiting genetic polymorphisms or haplotypes which indicate an increased risk for adverse drug reactions. In that case the drug dose should be lowered in a way that the risk for ADR is diminished. Also if the patient's response to drug administration is particularly high (or the patient is badly metabolizing the drug), the drug dose should be lowered to avoid the risk of ADR.

In turn if the patient's response to drug administration is low (or the patient is a particularly high metabolizer of the drug), and there is no evident risk of ADR, the drug dose should be raised to an efficacious level.

It is self evident that the ability to predict a patient's individual drug response should affect the formulation of a drug, i.e. drug formulations should be tailored in a way that they suit the different patient classes (low/high responder, poor/good metabolizer, ADR prone patients). Those different drug formulations may encompass different doses of the drug, i.e. the medicinal products contains low or high amounts of the active substance. In another embodiement of the invention the drug formulation may contain additional substances that facilitate the beneficial effects and/or diminish the risk for ADR (Folkers et al. 1991, US Pat. 5,316,765).

## Isolated Polymorphic Nucleic Acids, Probes, and Vectors

The present invention provides isolated nucleic acids comprising the polymorphic positions described herein for human genes; vectors comprising the nucleic acids; and transformed host cells comprising the vectors. The invention also provides probes which are useful for detecting these polymorphisms.

In practicing the present invention, many conventional techniques in molecular biology, microbiology, and recombinant DNA, are used. Such techniques are well known and are explained fully in, for example, Sambrook et al., 1989, Molecular

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Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; DNA Cloning: A Practical Approach, Volumes I and II, 1985 (D. N. Glover ed.); Oligonucleotide Synthesis, 1984, (M. L.Gait ed.); Nucleic Acid Hybridization, 1985, (Hames and Higgins); Ausubel et al., Current Protocols in Molecular Biology, 1997, (John Wiley and Sons); and Methods in Enzymology Vol. 154 and Vol. 155 (Wu and Grossman, and Wu, eds., respectively).

Insertion of nucleic acids (typically DNAs) comprising the sequences in a functional surrounding like full length cDNA of the present invention into a vector is easily accomplished when the termini of both the DNAs and the vector comprise compatible restriction sites. If this cannot be done, it may be necessary to modify the termini of the DNAs and/or vector by digesting back single-stranded DNA overhangs generated by restriction endonuclease cleavage to produce blunt ends, or to achieve the same result by filling in the single-stranded termini with an appropriate DNA polymerase.

Alternatively, any site desired may be produced, e.g., by ligating nucleotide sequences (linkers) onto the termini. Such linkers may comprise specific oligonucleotide sequences that define desired restriction sites. Restriction sites can also be generated by the use of the polymerase chain reaction (PCR). See, e.g., Saiki et al., 1988, Science 239:48. The cleaved vector and the DNA fragments may also be modified if required by homopolymeric tailing.

The nucleic acids may be isolated directly from cells or may be chemically synthesized using known methods. Alternatively, the polymerase chain reaction (PCR) method can be used to produce the nucleic acids of the invention, using either chemically synthesized strands or genomic material as templates. Primers used for PCR can be synthesized using the sequence information provided herein and can further be designed to introduce appropriate new restriction sites, if desirable, to facilitate incorporation into a given vector for recombinant expression.

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The nucleic acids of the present invention may be flanked by native gene sequences, or may be associated with heterologous sequences, including promoters, enhancers, response elements, signal sequences, polyadenylation sequences, introns, 5'- and 3'noncoding regions, and the like. The nucleic acids may also be modified by many means known in the art. Non-limiting examples of such modifications include methylation, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphoroamidates, carbamates, morpholines etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.). Nucleic acids may contain one or more additional covalently linked moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), intercalators (e.g., acridine, psoralen, etc.), chelators (e.g., metals, radioactive metals, iron, oxidative metals, etc.), and alkylators. PNAs are also included. The nucleic acid may be derivatized by formation of a methyl or ethyl phosphotriester or an alkyl phosphoramidate linkage. Furthermore, the nucleic acid sequences of the present invention may also be modified with a label capable of providing a detectable signal, either directly or indirectly. Exemplary labels include radioisotopes, fluorescent molecules, biotin, and the like.

The invention also provides nucleic acid vectors comprising the gene sequences or derivatives or fragments thereof of genes described in the Examles. A large number of vectors, including plasmid and fungal vectors, have been described for replication and/or expression in a variety of enkaryotic and prokaryotic hosts, and may be used for gene therapy as well as for simple cloning or protein expression. Non-limiting examples of suitable vectors include without limitation pUC plasmids, pET plasmids (Novagen, Inc., Madison, Wis.), or pRSET or pREP (Invitrogen, San Diego, Calif.), and many appropriate host cells, using methods disclosed or cited herein or otherwise known to those skilled in the relevant-art. The particular choice of vector/host is not critical to the practice of the invention.

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Suitable host cells may be transformed/transfected/infected as appropriate by any suitable method including electroporation, CaCl2 mediated DNA uptake, fungal or viral infection, microinjection, microprojectile, or other established methods. Appropriate host cells included bacteria, archebacteria, fungi, especially yeast, and plant and animal cells, especially mammalian cells. A large number of transcription initiation and termination regulatory regions have been isolated and shown to be effective in the transcription and translation of heterologous proteins in the various hosts. Examples of these regions, methods of isolation, manner of manipulation, etc. are known in the art. Under appropriate expression conditions, host cells can be used as a source of recombinantly produced peptides and polypeptides encoded by genes of the Examples. Nucleic acids encoding peptides or polypeptides from gene sequences of the Examples may also be introduced into cells by recombination events. For example, such a sequence can be introduced into a cell and thereby effect homologous recombination at the site of an endogenous gene or a sequence with substantial identity to the gene. Other recombination-based methods such as nonhomologous recombinations or deletion of endogenous genes by homologous recombination may also be used.

In case of proteins that form heterodimers or other multimers, both or all subunits have to be expressed in one system or cell.

The nucleic acids of the present invention find use as probes for the detection of genetic polymorphisms and as templates for the recombinant production of normal or variant peptides or polypeptides encoded by genes listed in the Examples.

Probes in accordance with the present invention comprise without limitation isolated nucleic acids of about 10-100 bp, preferably 15-75 bp and most preferably 17-25 bp in length, which hybridize at high stringency to one or more of the polymorphic sequences disclosed herein or to a sequence immediately adjacent to a polymorphic position. Furthermore, in some embodiments a full-length gene sequence may be

used as a probe. In one series of embodiments, the probes span the polymorphic positions in genes disclosed herein. In another series of embodiments, the probes correspond to sequences immediately adjacent to the polymorphic positions.

# 5 Polymorphic Polypeptides and Polymorphism-Specific Antibodies

The present invention encompasses isolated peptides and polypeptides encoded by genes listed in the Examples comprising polymorphic positions disclosed herein. In one preferred embodiment, the peptides and polypeptides are useful screening targets to identify cardiovascular drugs. In another preferred embodiments, the peptides and polypeptides are capable of eliciting antibodies in a suitable host animal that react specifically with a polypeptide comprising the polymorphic position and distinguish it from other polypeptides having a different sequence at that position.

- Polypeptides according to the invention are preferably at least five or more residues in length, preferably at least fifteen residues. Methods for obtaining these polypeptides are described below. Many conventional techniques in protein biochemistry and immunology are used. Such techniques are well known and are explained in Immunochemical Methods in Cell and Molecular Biology, 1987 (Mayer and Waler, eds; Academic Press, London); Scopes, 1987, Protein Purification: Principles and Practice, Second Edition (Springer-Verlag, N.Y.) and Handbook of Experimental Immunology, 1986, Volumes I-IV (Weir and Blackwell eds.).
- Nucleic acids comprising protein-coding sequences can be used to direct the ITT recombinant expression of polypeptides encoded by genes disclosed herein in intact cells or in cell-free translation systems. The known genetic code, tailored if desired for more efficient expression in a given host organism, can be used to synthesize oligonucleotides encoding the desired amino acid sequences. The polypeptides may be isolated from human cells, or from heterologous organisms or cells (including, but not limited to, bacteria, fungi, insect, plant, and mammalian cells) into which an

appropriate protein-coding sequence has been introduced and expressed. Furthermore, the polypeptides may be part of recombinant fusion proteins.

Peptides and polypeptides may be chemically synthesized by commercially available automated procedures, including, without limitation, exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. The polypeptides are preferably prepared by solid phase peptide synthesis as described by Merrifield, 1963, J. Am. Chem. Soc. 85:2149.

Methods for polypeptide purification are well-known in the art, including, without limitation, preparative disc-gel electrophoresis, isoelectric focusing, HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, and countercurrent distribution. For some purposes, it is preferable to produce the polypeptide in a recombinant system in which the protein contains an additional sequence tag that facilitates purification, such as, but not limited to, a polyhistidine sequence. The polypeptide can then be purified from a crude lysate of the host cell by chromatography on an appropriate solid-phase matrix. Alternatively, antibodies produced against peptides encoded by genes disclosed herein, can be used as purification reagents. Other purification methods are possible.

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The present invention also encompasses derivatives and homologues of the polypeptides. For some purposes, nucleic acid sequences encoding the peptides may be altered by substitutions, additions, or deletions that provide for functionally equivalent molecules, i.e., function-conservative variants. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of similar properties, such as, for example, positively charged amino acids (arginine, lysine, and histidine); negatively charged amino acids (aspartate and glutamate); polar neutral amino acids; and non-polar amino acids.

The isolated polypeptides may be modified by, for example, phosphorylation, sulfation, acylation, or other protein modifications. They may also be modified with

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a label capable of providing a detectable signal, either directly or indirectly, including, but not limited to, radioisotopes and fluorescent compounds.

The present invention also encompasses antibodies that specifically recognize the polymorphic positions of the invention and distinguish a peptide or polypeptide containing a particular polymorphism from one that contains a different sequence at that position. Such polymorphic position-specific antibodies according to the present invention include polyclonal and monoclonal antibodies. The antibodies may be elicited in an animal host by immunization with peptides encoded by genes disclosed herein or may be formed by in vitro immunization of immune cells. The immunogenic components used to elicit the antibodies may be isolated from human cells or produced in recombinant systems. The antibodies may also be produced in recombinant systems programmed with appropriate antibody-encoding DNA. Alternatively, the antibodies may be constructed by biochemical reconstitution of purified heavy and light chains. The antibodies include hybrid antibodies (i.e., containing two sets of heavy chain/light chain combinations, each of which recognizes a different antigen), chimeric antibodies (i.e., in which either the heavy chains, light chains, or both, are fusion proteins), and univalent antibodies (i.e., comprised of a heavy chain/light chain complex bound to the constant region of a second heavy chain). Also included are Fab fragments, including Fab' and F(ab).sub.2 fragments of antibodies. Methods for the production of all of the above types of antibodies and derivatives are well-known in the art and are discussed in more detail below. For example, techniques for producing and processing polyclonal antisera are disclosed in Mayer and Walker, 1987, Immunochemical Methods in Cell and Molecular Biology, (Academic Press, London). The general methodology for making monoclonal antibodies by hybridomas is well known. Immortal antibodyproducing cell lines can be created by cell fusion, and also by other techniques such as direct transformation of B lymphocytes with oncogenic DNA, or transfection with Epstein-Barr virus. See, e.g., Schreier et al., 1980, Hybridoma Techniques; U.S. Pat. Nos. 4,341,761; 4,399,121; 4,427,783; 4,444,887; 4,466,917; 4,472,500; 4,491,632; and 4,493,890. Panels of monoclonal antibodies produced against peptides encoded

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by genes disclosed herein can be screened for various properties; i.e. for isotype, epitope affinity, etc.

The antibodies of this invention can be purified by standard methods, including but not limited to preparative disc-gel electrophoresis, isoelectric focusing, HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, and countercurrent distribution. Purification methods for antibodies are disclosed, e.g., in The Art of Antibody Purification, 1989, Amicon Division, W. R. Grace & Co. General protein purification methods are described in Protein Purification: Principles and Practice, R. K. Scopes, Ed., 1987, Springer-Verlag, New York, N.Y.

Methods for determining the immunogenic capability of the disclosed sequences and the characteristics of the resulting sequence-specific antibodies and immune cells are well-known in the art. For example, antibodies elicited in response to a peptide comprising a particular polymorphic sequence can be tested for their ability to specifically recognize that polymorphic sequence, i.e., to bind differentially to a peptide or polypeptide comprising the polymorphic sequence and thus distinguish it from a similar peptide or polypeptide containing a different sequence at the same position.

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#### Kits

As set forth herein, the invention provides diagnostic methods, e.g., for determining the identity of the allelic variants of polymorphic regions present in the gene loci of genes disclosed herein, wherein specific allelic variants of the polymorphic region are associated with cardiovascular diseases. In a preferred embodiment, the diagnostic kit can be used to determine whether a subject is at risk of developing a cardiovascular disease. This information could then be used, e.g., to optimize treatment of such individuals.

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In preferred embodiments, the kit comprises a probe or primer which is capable of hybridizing to a gene and thereby identifying whether the gene contains an allelic variant of a polymorphic region which is associated with a risk for cardiovascular disease. The kit preferably further comprises instructions for use in diagnosing a subject as having, or having a predisposition, towards developing a cardiovascular disease. The probe or primers of the kit can be any of the probes or primers described in this file.

Preferred kits for amplifying a region of a gene comprising a polymorphic region of interest comprise one, two or more primers.

# Autibody-based diagnostic methods and kits:

The invention also provides antibody-based methods for detecting polymorphic patterns in a biological sample. The methods comprise the steps of: (i) contacting a sample with one or more antibody preparations, wherein each of the antibody preparations is specific for a particular polymorphic form of the proteins encoded by genes disclosed herein, under conditions in which a stable antigen-antibody complex can form between the antibody and antigenic components in the sample; and (ii) detecting any antigen-antibody complex formed in step (i) using any suitable means known in the art, wherein the detection of a complex indicates the presence of the particular polymorphic form in the sample.

Typically, immunoassays use either a labelled antibody or a labelled antigenic component (e.g., that competes with the antigen in the sample for binding to the antibody). Suitable labels include without limitation enzyme-based, fluorescent, chemiluminescent, radioactive, or dye molecules. Assays that amplify the signals from the probe are also known, such as, for example, those that utilize biotin and avidin, and enzyme-labelled immunoassays, such as ELISA assays.

The present invention also provides kits suitable for antibody-based diagnostic applications. Diagnostic kits typically include one or more of the following components:

- Polymorphism-specific antibodies. The antibodies may be pre-labelled; alternatively, the antibody may be unlabelled and the ingredients for labelling may be included in the kit in separate containers, or a secondary, labelled antibody is provided; and
- 10 (ii) Reaction components: The kit may also contain other suitably packaged reagents and materials needed for the particular immunoassay protocol, including solid-phase matrices, if applicable, and standards.
- The kits referred to above may include instructions for conducting the test.

  Furthermore, in preferred embodiments, the diagnostic kits are adaptable to high-throughput and/or automated operation.

## **Drug Targets and Screening Methods**

- According to the present invention, nucleotide sequences derived from genes disclosed herein and peptide sequences encoded by genes disclosed herein, particularly those that contain one or more polymorphic sequences, comprise useful targets to identify cardiovascular drugs, i.e., compounds that are effective in treating one or more clinical symptoms of cardiovascular disease. Furthermore, especially when a protein is a multimeric protein that are build of two or more subunits, is a combination of different polymorphic subunits very useful.
- Drug targets include without limitation (i) isolated nucleic acids derived from the genes disclosed herein, and (ii) isolated peptides and polypeptides encoded by genes disclosed herein, each of which comprises one or more polymorphic positions.

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# In vitro screening methods:

In one series of embodiments, an isolated nucleic acid comprising one or more polymorphic positions is tested in vitro for its ability to bind test compounds in a sequence-specific manner. The methods comprise:

- (i) providing a first nucleic acid containing a particular sequence at a polymorphic position and a second nucleic acid whose sequence is identical to that of the first nucleic acid except for a different sequence at the same polymorphic position;
- (ii) contacting the nucleic acids with a multiplicity of test compounds under conditions appropriate for binding; and
- 15 (iii) identifying those compounds that bind selectively to either the first or second nucleic acid sequence.

Selective binding as used herein refers to any measurable difference in any parameter of binding, such as, e.g., binding affinity, binding capacity, etc.

In another series of embodiments, an isolated peptide or polypeptide comprising one or more polymorphic positions is tested in vitro for its ability to bind test compounds in a sequence-specific manner. The screening methods involve:

- 25 (i) providing a first peptide or polypeptide containing a particular sequence at a polymorphic position and a second peptide or polypeptide whose sequence is identical to the first peptide or polypeptide except for a different sequence at the same polymorphic position;
- 30 (ii) contacting the polypeptides—with a multiplicity of test compounds under conditions appropriate for binding; and

- (iii) identifying those compounds that bind selectively to one of the nucleic acid sequences.
- In preferred embodiments, high-throughput screening protocols are used to survey a large number of test compounds for their ability to bind the genes or peptides disclosed above in a sequence-specific manner.
  - Test compounds are screened from large libraries of synthetic or natural compounds. Numerous means are currently used for random and directed synthesis of saccharide, peptide, and nucleic acid based compounds. Synthetic compound libraries are commercially available from Maybridge Chemical Co. (Trevillet, Cornwall, UK), Comgenex (Princeton, N.J.), Brandon Associates (Merrimack, N.H.), and Microsource (New Milford, Conn.). A rare chemical library is available from Aldrich (Milwaukee, Wis.). Alternatively, libraries of natural compounds in the form of bacterial, flungal, plant and animal extracts are available from e.g. Pan Laboratories (Bothell, Wash.) or MycoSearch (N.C.), or are readily producible. Additionally, natural and synthetically produced libraries and compounds are readily modified through conventional chemical, physical, and biochemical means.

In vivo screening methods

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Intact cells or whole animals expressing polymorphic variants of genes disclosed herein can be used in screening methods to identify candidate cardiovascular drugs.

In one series of embodiments, a permanent cell line is established from an individual exhibiting a particular polymorphic pattern. Alternatively, cells (including without limitation mammalian, insect, yeast, or bacterial cells) are programmed to express a gene comprising one or more polymorphic sequences by introduction of appropriate DNA. Identification of candidate compounds can be achieved using any suitable assay, including without limitation (i) assays that measure selective binding of test

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compounds to particular polymorphic variants of proteins encoded by genes disclosed herein; (ii) assays that measure the ability of a test compound to modify (i.e., inhibit or enhance) a measurable activity or function of proteins encoded by genes disclosed herein; and (iii) assays that measure the ability of a compound to modify (i.e., inhibit or enhance) the transcriptional activity of sequences derived from the promoter (i.e., regulatory) regions of genes disclosed herein.

In another series of embodiments, transgenic animals are created in which (i) one or more human genes disclosed herein, having different sequences at particular polymorphic positions are stably inserted into the genome of the transgenic animal; and/or (ii) the endogenous genes disclosed herein are inactivated and replaced with human genes disclosed herein, having different sequences at particular polymorphic positions. See, e.g., Coffman, Semin. Nephrol. 17:404, 1997; Esther et al., Lab. Invest. 74:953, 1996; Murakami et al., Blood Press. Suppl. 2:36, 1996. Such animals can be treated with candidate compounds and monitored for one or more clinical markers of cardiovascular status.

The following are intended as non-limiting examples of the invention.

#### 20 Material and Methods

Genotyping of patient DNA with the Pyrosequencing<sup>TM</sup> Method as described in the patent application WO 9813523:

First a PCR is set up to amplify the flanking regions around a SNP. Therefor 2 ng of genomic DNA (patient sample) are mixed with a primerset (20 – 40 pmol) producing a 75 to 320 bp PCR fragment with 0,3 to 1 U Qiagens Hot Star Taq Polymerase<sup>TM</sup> in a total volume of 20 μL. One primer is biotinylated depending on the direction of the sequencing primer. To force the biotinylated primer to be incorporated it is used 0,8 fold.

For primer design, programms like Oligo 6<sup>TM</sup> (Molecular Biology Insights) or Primer Select<sup>TM</sup> (DNAStar) are used. PCR setup is performed by a BioRobot 3000 <sup>TM</sup> from Qiagen: PCR takes place in T1 or Tgradient Thermocyclers <sup>TM</sup> from Biometra.

The whole PCR reaction is transferred into a PSQ plate TM (Pyrosequencing) and prepared using the Sample Prep Tool TM and SNP Reagent Kit TM from Pyrosequencing according to their instructions.

#### Preparation of template for Pyrosequencing TM:

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Sample preparation using PSQ 96 Sample Prep Tool:

- 1. Mount the PSQ 96 Sample Prep Tool Cover onto the PSQ 96 Sample Prep Tool as follows: Place the cover on the desk, retract the 4 attachment rods by separating the handle from the magnetic rod holder, fit the magnetic rods into the holes of the cover plate, push the handle downward until a click is heard. The PSQ 96 Sample Prep Tool is now ready for use.
- 2. To transfer beads from one plate to another, place the covered tool into the PSQ 96 Plate containing the samples and lower the magnetic rods by separating the handle from the magnetic rod holder. Move the tool up and down a few times then wait for 30-60 seconds. Transfer the beads into a new PSQ 96 plate containing the solution of choice.
- 25 3. Release the beads by lifting the magnetic rod holder, bringing it together with the handle. Move the tool up and down a few times to make sure that the beads are released.

All steps are performed at room temperature unless otherwise stated.

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### Immobilization of PCR product:

Biotinylated PCR products are immobilized on streptavidin-coated Dynabeads<sup>TM</sup> M-280 Streptavidin. Parallel immobilization of several samples are performed in the PSQ 96 Plate.

- Mix PCR product, 20 μl of a well optimized PCR, with 25 μl 2X BW-buffer II. Add 60-150 μg Dynabeads. It is also possible to add a mix of Dynabeads and 2X BW-buffer II to the PCR product yielding a final BW-buffer II concentration of approximately 1x.
- Incubate at 65°C for 15 min agitation constantly to keep the beads dispersed.
   For optimal immobilization of fragments longer than 300 bp use 30 min incubation time.

#### Strand separation:

- 4. For strand separation, use the PSQ 96 Sample Prep Tool to transfer the beads with the immobilized sample to a PSQ 96 Plate containing 50  $\mu$ l 0.50 M NaOH per well. Release the beads.
- 5. After approximately 1 min, transfer the beads with the immobilized strand to a PSQ 96 Plate containing 99  $\mu$ l 1x Annealing buffer per well and mix thoroughly.
- 6. Transfer the beads to a PSQ 96 Plate containing 45 µl of a mix of lx.

  Annealing buffer and 3-15 pmoles sequencing primer per well.
  - 7. Heat at 80°C for 2 minutes in the PSQ 96 Sample Prep Thermoplate and move to room temperature.
  - 8. After reaching room temperature, continue with the sequencing reaction.

#### Sequencing reaction:

- 1. Choose the method to be used ("SNP Method") and enter relevant information in the PSQ 96 Instrument Control software.
- 5 2. Place the cartridge and PSQ 96 Plate in the PSQ 96 Instrument.
  - 3. Start the run.

#### Genotyping using the ABI 7700/7900 instrument (TaqMan)

SNP genotypisation using the TaqMan (Applied Biosystems/Perkin Elmer) was performed according to the manufacturer's instructions. The TaqMan assay is discussed by Lee et al., Nucleic Acids Research 1993, 21: 3761-3766.

#### Genotyping with a service contractor:

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Qiagen Genomics, formerly Rapigene, is a service contractor for genotyping SNPs in patient samples. Their method is based on a primer extension method where two complementary primers are designed for each genotype that are labeled with different tags. Depending on the genotype only one primer will be elongated together with a certain tag. This tag can be detected with mass spectrometry and is a measure for the respective genotype. The method is described in the following patent: "Detection and identification of nucleic acid molecules - using tags which may be detected by non-fluorescent spectrometry or potentiometry" (WO 9727325).

#### **Examples**

To exemplify the present invention and it's utility (the imaginary) baySNP 28 will be used in the following:

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The nucleotide polymorphism found for baySNP 28 (e.g. C to T exchange) and the gene in which it presumably resides can be read from table 3. baySNP 28 was genotyped in various patient cohorts using primers as described in table 2. As a result the following number of patients carrying different genotypes were found (information combined from tables 3 and 5a):

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	Cohort	Total	Genotype 11 "CC"	Genotype 12	
28	HELD_FEM_HIRESP	12	1	2	"TT"
28	HELD_FEM_LORESP	.22	3	7 12	7

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When comparing the number of female patients exhibiting a high response to statin therapy (HELD\_FEM\_HIRESP) with the control cohort (HELD\_FEM\_LORESP) it appears that the number of low responders carrying the CT genotype is increased. This points to a lower statin response among female individuals with the CT genotype. Applying statistical tests on those findings the following p-values were obtained (data taken from table 5b):

BAYSNP 28	COMPARISON	GTYPE CPVAL	GTYPE XPVAL	GTYPE LRPVAL
	HELD_FEM_EFF	0,0506	0,0508	0,0442

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As at least one of the GTYPE p values is below 0,05 the association of genotype and statin response phenotype is regarded as statistically significant. I.e. the analysis of a patient's genotype can predict the response to statin therapy. In-more-detail-one-can-

calculate the relative risk to exhibit a certain statin response phenotype when carrying a certain genotype (data taken from table 6a):

BAYSNP	COMPARISON	COMPARISON GTYPE1		GTYPE2 GTYPE3			RR3
28	HELD_FEM_EFF	CC	CT	TT	0,68	0,29	3,38

In case of baySNP 28 the risk to exhibit a high responder phenotype is 3,38 times higher when carrying the TT genotype. This indicates that a TT polymorphism in baySNP 28 is an independent risk factor for high statin response in females. On the other hand carriers of a CT or CC genotype have a reduced risk of being a high responder.

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In addition statistical associations can be calculated on the basis on alleles. This calculation would identify risk alleles instead of risk genotypes.

In case of baySNP 28 the following allele counts were obtained (data combined from tables 3 and 5a):

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baySNP	Cohort	Total	Allele 1	Allele 2
•			" <b>C</b> ".	"T"
28	HELD_FEM_HIRESP	12	4	20
28	HELD_FEM_LORESP	22.	18	26

When comparing the number of female patients with high statin response (HELD\_FEM\_HIRESP) with the control cohort (HELD\_FEM\_LORESP) it appears that the number of high responders carrying the T allele is increased, whereas the number of high responders carrying the C allele is diminished. This points to a higher statin response among female individuals with the T allele. Applying statistical tests on those findings the following p-values were obtained (data taken from table 5b):

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	BAYSNP		ALLELE CPVAL	ALLELE XPVAL	ALLELE LRPVAL
l	28	HELD_FEM_EFF	0,0411	. 0,0579	0,0349

As at least one of the ALLELE p values is below 0,05 the association of allele and statin response phenotype is regarded as statistically significant (in this example significant p values were obtained from two statistical tests). I.e. also the analysis of a patient's alleles from baySNP 28 can predict the extend of statin response. In more detail one can calculate the relative risk to exhibit a certain statin response phenotype when carrying a certain allele (data taken from table 6b):

	baySNP	ATTA				•
	Allele 1	Allele 2	COMPARISON	RRI	RR2	
	28	С	T	TITT D TITT		
			_ *	HELD_FEM_EFF	0,42	2,39
						_,00

10 In case of baySNP 28 the risk to exhibit a high responder phenotype is 2,39 times higher when carrying the T allele. This indicates that the T allele of baySNP28 is an independent risk factor for a high statin response in females. In other words those patients should receive lower doses of statins in order to avoid ADR. However due to their 'high responder' phenotype they will still benefit from the drug. In turn carriers of the C allele should receive higher drug doses in order to experience a benefical 15 therapeutic effect.

Another example is (the imaginary) baySNP 29, which is taken to exemplify polymorphisms relevant for adverse drug reactions. baySNP 29 was found significant when comparing male patients with severe ADR to the respective controls (as defined in table 1b).

The relative risk ratios for the genotypes AA, AG and GG were as follows (data taken from table 6a):

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BAYSNP	COMPARISON	COMPARISON GTYPE1 GT		GTYPE3	RR1	RR2	RR3
29	HELD_MAL_ADR5ULN	AA	· AG	· GG	3,15	0,66	0,32

In this case male patients carrying the AA genotype have a 3,15 times higher risk to suffer from ADR. In other words those patients should either receive lower doses of statins or switch to an alternative therapy in order to avoid ADR. On the other hand male patients with AG or GG genotypes appear to be more resistant to ADR and hence better tolerate statin therapy.

As can be seen from the following tables some of the associations that are disclosed in the present invention are indicative for more than one phenotype. Some baySNPs can for example be linked to ADR, but also to the risk to suffer from CVD (table 6).

#### Sequences

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The sequence section contains all phenotype associated ('PA') SNPs and adjacent genomic sequences. The position of the polymorphisms that were used for the association studies ('baySNP') is indicated. Sometimes additional variations are found in the surrounding genomic sequence, that are marked by it's respective IUPAC code. Although those surrounding SNPs were not explicitly analyzed, they likely exihibit a similar association to a phenotype as the baySNP (due to linkage disequillibrium, Reich D.E. et al. Nature 411, 199-204, 2001).

Table 1a Definition of "good" and "bad" serum lipid levels

	"Good"	"Bad"
LDL-Cholesterol [mg/dL]	125 -150	170 - 200
Cholesterol [mg/dL]	190 - 240	265 - 315
HDL-Cholesterol [mg/dL]	60 -105	30 - 55
Triglycerides [mg/dL]	45 - 115	170 – 450

<u>Table 1b</u> Definition of drug response phenotypes

Low responder	Decrease of serum LDL of at least 10% and at most 50% upon administration of 0.8 mg Continued in 10% and at most 50% upon
<del> </del>	I TO MARION CONTROL OF THE CONTR
High responder	Decrease of serum LDL of at least 500% upon administration
Very low	
	Decrease of serum LDL of at least 10% and at most 3500
responder	
Very high	Decrease of serum LDL of at least 55% man additional
responder	
Ultra low	Decrease of serum LDI, of at least 100/
responder	The second of th
Ultra high	Decidase of serum Lill, of at least 60% upon administration
responder	0.4 mg Cerivastatin (female patients)
-	No diagnosis of muscle cramps, muscle pain, muscle weakness,
	myalgia or myopathy muscle weakness,
Tolerant patient	AND
	serum CK levels below 70 mg/41 :
	serum CK levels below 70 mg/dl in women and below 80 mg/dl in men.
ADR patient	
(CK increase at	Diagnosis of muscle cramps, muscle pain, muscle weakness, myalgia or myopathy
least 2×ULN)	OR
	serum CK levels higher than 140
	serum CK levels higher than 140 mg/dl in women and 160 mg/dl in men.
Advanced ADR	
patient [ADR3]	
advanced CK	Serum CK levels higher than 210 mg/dl in women and 240 mg/dl in men
ncrease, at least	in men
×ULN)*	·
evere ADR	
atient [ADR 5]	
severe CK	Serum CK levels higher than 350 mg/dl in women and 400 mg/dl
icrease, at least	in men south and 400 mg/dl
×ULN)*	,
	or the cohorts for all

<sup>\*:</sup> When assembling the cohorts for advanced and severe ADR we focused on the CK serum levels as those provide a more independent measure of statin related ADR.

<u>Table 1c</u> Definition of "high" and "low" serum HDL cholesterol levels

	Male	Female
	individuals	individuals
,High' HDL-Cholesterol [mg/dL]	>=80	>=104
,Low' HDL-Cholesterol [mg/dL]	<=35	<=37

An informed consent was signed by the patients and control people. Blood was taken by a physician according to medical standard procedures.

Samples were collected anonymous and labeled with a patient number.

DNA was extracted using kits from Qiagen.

# <u>Table 2</u> Oligonucleotide primers used for genotyping

Depending on the method used for genotyping different oligonucleotides were utilized. The table lists the various methods and primer sets that were used for this invention. Primers were designed using suitable programs like Primer Express<sup>TM</sup> (Applied Biosystems, Darmstadt, Germany) or Oligo<sup>TM</sup> (Molecular Biology Insights, Inc., Cascade, CO, USA).

Method	No. of oligonucleotides	Type of oligonucletides
Mass Spectrometry	4	2 Primers for preamplification of the genomic fragment, 2 allele specific primers with additional tag sequences for subsequent allele spec. PCR
Pyrosequencing™	3	2 Primers for preamplification of the genomic fragment (one biotinylated), 1 sequencing primer
ТаqМап	4	2 Primers for amplification of the genomic fragment, 2 allele specific probes carrying different fluorochromes (VIC, FAM) and a quencher.  Preferably the allele specific probes have a minor groove binder (MGB) attached (Kutyavin et al., Nucleic Acids Research 2000, 28:655-661).

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# PA SNPs, SNP classes and putative PA genes

Table 3

The baySNP number refers to an internal numbering of the PA SNPs. Listed are the different polymorphisms found in our association study. Also fion the association study we defined SNP classes; with ADR being adverse drug reaction related, with EFF being drug efficacy related and CVD being cardiovascular disease related. ADR3 and ADR5 relate to advanced and severe ADR, whereas VEFF and UEFF relate to very high/low and ultra high/low drug efficacy (see table 1b). Also accession numbers and descriptions of those gene loci are given that are most those skilled in the art in the Genbank database. The term 'SECONDARY' marks SNPs that do not reside inside the respective gene, but in homologous to the PA genes as listed in the sequences section (see below). Homologous genes and their accession numbers could be found by it's proximity. Null: not defined.

	Joint Industrial TVAN	arcing 1 LAM   protein (11AM1) mRNA	ucing 11AM1 protein (TIAM1) mRNA	c subuait (P1 form)			I) mknA, complete cds.	1) JUNNA, complete cds. tyl-Coenzyme A Ivase (hydroxymethyl.		ryl-Coenzyme A lyase (hydroxymethyl-		yl-Coenzyme A lyase (hydroxymethyl-		
Venio e Deserronon	Human T-lymphoma invasion and meteracic industries TAN	Human T-lymhoma invasion and materials	H. saniens pene for mito-hood-in 4 m	Human beta adaptin mRNA complete 24.	H.sapiens dek mRNA	Human flavin-containing monocourage (E) (C)	Human flavin-containing monocococo (EMO)	Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A Ivase (hydroxymethyl	glutaricaciduria) (HMGCL), mRNA	Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethyl-	glufaricaciduria) (HMGCL), mRNA	Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A Iyase (hydroxymethyl.	glutaricaciduria) (HMGCL), nıRNA	
	HS162961	HS162961	X69907	M34175	X64229	M64082	M64082	NM 000191		161000 MN		NM 000193		
Common	පි	8	99	E	ŢŢ.	A.A.	₹ ¥	₩ ₩		₽¥		Ą	•	
Subjection 2	AG	AG	8	CT	ر <del>ر</del>	AG	AG .	AG		AG		AG		
	¥	*	ខ	ខ	ည	99	99	8		99		99		
-	CAD	ADR3	CVD	CVD	cvo	ADRS	ADR3	ADRS		ADR3		ADR	-	
BANSIN	67	29	25	57	118	137	137	179		179		179		

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NGRIGE DESCRIPTION SERVICE CONTRACTOR OF THE SERVICE OF THE SERVIC	Human beat-shock protein HSP70B' gene	Human heat-shock protein HSP70B' gene	Human beat-shock protein HSP70B' gene	H. sapiens SCA1 mRNA for ataxin	Human tumor necrosis factor type 1 receptor associated protein (TRAP1) mRNA, partial cds.	H.sapiens mRNA for DLG2	Human flavin-containing monooxygenase (FMO1) mRNA, complete cds.	Homo sapiens mRNA for smooth muscle myosin heavy chain, partial eds.	Human lamin B2 (LAMB2) gene and ppvl gene sequence.	Human methylenetetrahydrofolate dehydrogenase- methenyltetrahydrofolate	cyclohydrolase-formylterrahydrofolate synthetase mRNA, complete cds.	Homo sapiens methionine adenosyltransferase alpha subunit gene fragment.	CALCIUM-TRANSPORTING ATPASE PLASMA MEMBRANE, ISOFORMS 3A/3B (EC	3.6.1.38) (CALCIUM PUMP) (PMCA3).	Human vascular endothelial growth factor gene, exon 1.	Homo sapiens WNT1 inducible signaling pathway protein ! (WISP1) gene, promoter and	partial cds.	Homo sapiens (clones lambda gMHC 1,2,3 and 4) beta-myosin heavy chain (MYH7) gene,	complete cds.	Homo sapiens lipoprotein lipase precursor, gene, partial cds.	Human lissue factor gene, complete cds.	Homo sapieus mRNA for diacylglycerol kinase della, complete cds.	Human protein C inhibitor gene, complete cds.	
100	34	X51757	X51757	X79204	U12595	X82895	M64082	D10667	M94363	. J04031		143509	016720	,	M63971	AF223404		M57965	2	AF050163	102846	D73409	M64880	
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A DISCRIPTION SET STATEMENT OF THE SET OF TH	Human calmodulin mbMA	Human calmodulin mBNA	Fuman calmodulin mRNA complete cus.	Human Na. KATPase submit alaba 2 (Armetan)	Human Na. K-A TPase calancie alpha 2 (ATF 142) gene, complete cds.	Human Na K-ATPage culturation of the complete cds.	Human apolinonrotein A.F. and C. III.	Human apolinonrotein A. J. and C. III.	Human apolipoprotein A - I and C-III comes commutes 23	Hunan cardiac myosin heavy chein mDNA 2:	Homo sapiens B94 pmtein mRNA commissions.	Haniens many for activity but of the	H. saniens APXT mRNIA	H saniene A P. 2 hete ware	Saniene mBNA for all a t	Home canions (2011 - 1011)	Homo caniene CDV7	Homo saniens GPV1 mPNA for all the control of the c	Homo saniens GPVI mPNA 61	Homo saniens GPVI mBNA for allocate 1.	Homo sapiens GPV/ mPNA for allered Blycoprotein VI-3, complete cds.	Homo sapiens GPVI mRNA for allies of	Human protein C inhibitor gene complete cds.	סייין עלייין עליי
(PEZZ   NOBLAR	J04046	304046	J04046	105096	105096	105096	100098	100098	36000f	MI7712	M92357	X82540					T	1.					M64880 H	
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BAKSIN	1757	1757	1757	1765	1767	1367	1837	1837	1837	1854	. 1862	2085	2093	2109	2124	2140	2140	2140	2140	2141	2141	2141	2186	
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GTOPPEL ST. INGBIE HIDESCRIPTION	M64880 Human protein Cinhibitor gene, complete eds.	M21616 Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	M21616 Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	M21616 Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	L36033 Human pre-B cell stimulating factor homologue (SDF1b) mRNA, complete cds.	M15395 Human leukocyte adhesion protein (LFA-1/Mac-1/p150,95 family) beta subunit mRNA.	X87872 H.sapiens mRNA for hepatocyte nuclear factor 4c	AB021744 Homo sapiens XIIIA gene for coagulation factor XIII A subunit, promoter sequence.	M11309 Human coagulation factor IX mRNA, complete cds.	M63971 Human vascular endothelial growth factor gene, exon 1.	M63971 Human vascular endothelial growth factor gene, exon 1.	M63971 Human vascular endothelial growth factor gene, exon 1.	M63971 Human vascular endothelial growth factor gene, exon 1.	AJ246000 Homo sapiens mRNA for leucocyte adhesion receptor, L-selectin	Q92679 BETA-MYOSIN HEAVY CHAIN.	M15856 Human lipoprotein Lipase mRNA, complete cds.	M18082 Human plasminogen activator inhibitor 2 (PAI-2) mRNA, complete cds.	AF084225 Homo sapiens cytochrome P450 2E1 (CYP2E1) mRNA, partial cds.	D63807 Human mRNA for lanosterol synthase, complete cds.	D63807 Human mRNA for lanosterol synthase, complete cds.	104501 Human muscle glycogen synthase mRNA, complete cds.	J04501 Human muscle glycogen synthase mRNA, complete cds.	U49248 ABCC2: ATP-binding cassette, sub-family C (CFTRMRP), member 2
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DAYSNE	2187	2192	2192	2192	2203	2217	2281	2284	2290	2327	2327	2327	2327	2353	2371	2376	2401	2463	2755	2755	2925	2925	3043

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139211	1_	VEFF	11	AT	*	L31573	Human sulfite oxidase mRNA, complete ede
NE		VEFF	ည	9	99	L39211	Homo supjeus mitochandrial camitica activities
CC   CG   GG   L41162     R5   CC   AC   AA   BC006394     R5   CC   AC   AA   BC012063     R5   CC   AC   AA   BC012063     R5   CC   AC   AA   BC010006     R5   CC   AC   AC   BC000006     R5   AA   AT   TT   BC000006     R5   AA   AT   AT   AT     R5   AA   AT   AT     R5   AA   AT   AT     R5   AA   AT   AT     R5   AA     R5   AA		ADRS	ဗ	8	Ilua	L40027	Homo samens a luncated at the complete cds.
TT   CT   CC   L41668     R3   CC   AC   AA   BC006394     R3   CC   AC   AA   BC006394     D   CC   CG   mull   U12595   H   F   GG   GT   TT   U17195   H   F   CC   AC   AA   BC012063   H   TT   CT   CC   BC000010   H   AA   AT   TT   BC000006   H   AA   AT   TT   BC000006   H   AA   AT   TT   BC000006   H   GG   AG   AA   X76228   H		CVD	ე	93	99	L41162	Homo saniens collocan alaba 2
R3         CC         AC         AA         BC006394           D         CC         AA         BC006394         In I		ADR	Ħ	ב	8	L41668	Homo sapiens UDP-galactose-4-enimerse (GAIE) mNNA, complete cds.
R3         CC         AC         AA         BC006394           D         CC         CG         mull         U12595           F         GG         GT         TT         U12595           F         GG         GT         TT         U17195           F         CC         AA         BC012063         R           F         CC         AA         BC000006         B           AA         AT         TT         BC000006         B           AA         AT         TT         BC000006         B           AA         AT         TT         BC000006         B           GG         AG         AA         X76228         B           GG         AG         AA         X76228         B           GG         AG         AA         NM_000755         B		ADRS	8	AC	¥₩	BC0063;34	Homo sapiens, COX10 (yeast) homolog, cytochrome c oxidase assembly protein (heme A: farnesyltransferase)
D         CC         CG         пиll         U12595           F         GG         GT         TT         U12595           F         CC         AA         AT         U17195           F         CC         AA         BC012063           B         AA         AT         TT         BC000006           B         AA         AT         TT         BC000006         B           B         AA         AT         TT         BC000006         B           GG         AG         AA         X76228         B		ADR3	8	AC	₩	BC006394	Homo sapiens, COX10 (yeast) homolog, cytochrome c oxidase assembly protein (heme A:
F         GG         GT         TT         U12595           F         GG         GT         TT         U17195           F         CC         AC         AA         BC012063           B         TT         CC         BC000006         B           AA         AT         TT         BC000006         B           GG         AA         AT         TT         BC000006         B           GG         AG         AA         X76228         B           GG         AG         AA         NM_000755         B	<u> </u>	GYD	႘	8	llun ·	U12595	Hunsa timor assures forces
F GG GT TT U17195  F CC AC AA BC012063  TT CT CC BC000011  AA AT TT BC000006  AA AT TT BC000006  GG AG AA X76228 F		CAD	A'A	AT		U12595	Human tumor necrosis factor time 1
F         CC         AC         AA         BC012063           TT         CT         BC0000011         BC000006         BC000006           AA         AT         TT         BC000006         BC000006           AA         AT         TT         BC000006         BC000006           GG         AG         AA         X76228         BC000006           GG         AG         AA         AN_000755         BC000755	=	UEFF	පි	GT	TL	U17195	Homo sapiens A-kinase anchor protein (AKAP100) mRNA complete of
TT         CT         CC         BC0000011           AA         AT         TT         BC000006           AA         AT         TT         BC000006           GG         AG         AA         X76228           BG         AG         AA         NM_000755		UEFF	8	AC	\$		Homo sapiens, Similar to retinoid X receptor, gamma, clone MGC:19909 IMAGE:4635470, nRNA, complete cds.
AA         AT         TT         BC000006           AA         AT         TT         BC000006           GG         AG         AA         X76228           GG         AG         AA         NM_000755		CVD	Ė	ت ت	8		iomo sapiens, mevalonate (diphospho) decarboxylase, clone MGC:1701 IMAGE:3505156,
AA         AT         TT         BC000006           GG         AG         AA         X76228           GG         AG         AA         NM_000755	<u> </u>	ADR3	AA A	AT	II	T	forms conjugated ATD.
GG         AG         AT         TT         BC000006           GG         AG         AA         X76228           GG         AG         AA         X76228           GG         AG         AA         X76228           GG         AG         AA         X76228           GG         AG         AA         NM_000755	<u> </u>	ADR	*	AT	F	$\top$	forms sepretable A I raise, Na+/K+ transporting, beta 1 polypeptide
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484	ADR	טט	AO	ĄĄ	NM 000753	Homo sapiens camitine acetyltransferase (CRAT), nuclear gene encoding mitochondrial
		}				protein, transcript variant 1, mRNA
4545	FRUA	ยูย	Ą	. 44	NPA 000755	Homo sapiens camitine acetyltransferase (CRAT), nuclear gene encoding mitochondrial
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2	·	3	2		700	protein, transcript variant 1, mRNA
4668	ADRS	පි	AC	ΑA	HSKINAANP	H.sapiens mRNA for kinase A anchor protein
4669	EFF	ප	ರ	E	HSKINAANP	H.sapieus mRNA for kinase A anchor protein
4718	CVD	99	PΑG	₩ ¥	V09862	H. sapiens mRNA for legumain
4818	CAD	99	AG.	AA	AJ276181	Homo sapiens partial ZNF202 gene for zinc finger protein homolog, exon 5
4827	ADRS	AA	AG	99	L07033	Human hydroxymethylglutaryl-CoA jyase mRNA, complete cds.
4838	CVD	A.A	ΑG	99	L08246	Human myeloid cell differentiation protein (MCL.1) mRNA.
4856	CVD	GG	AG	Ilua	L11669	Human tetracycline transporter-like protein mRNA, complete cds.
4868	ADR	TT	ಶ	ည	U83661	Homo sapiens multidrug resistance protein 5 (MRP5) mRNA, complete cds
4868	ADRS	TT	נז	8	U83661	Homo sapiens multidrug resistance protein 5 (MRP5) mRNA, complete cds
4887	CAD	23	AC	YV.	AC004264	Homo sapiens PAC clone RP1-102K2 from 22q12.1-qter, complete sequence.
4912	CVD	gg	ΨG	AA A	M63971	Human vascular endothelial growth factor gene, exon 1.
4951	ADR3	99	AG	₩	AF091582	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11
4951	ADRS	gg	. AG	- AA -	AF091582	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11
4951	ADR	99	. AG	₩	AF091582	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11
4952	ADR3	TT	<del>ل</del> ا	8	AF091582	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11
4952	ADRS	Ħ	5	23	AF091582	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11
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22.	Homo sapiens cytochrome P450 (CYP4F8) mRNA, complete cds.	Homo sapiens cytochrome P450 (CYP4F8) mRNA, complete cds	Homo sapiens mRNA for calphobingin II commission A.	Human platelet-derived grounds 6.	Human plateled Actions	Himan state of A	Himan mRNA for continuous stockton receptor alpha (PDGFRA) mRNA, complete cds.	Human archinocests: D. P. S. S.	Human colin comit	Human calmedulin mDNA	Human microtribule generals	U	nutrian micrombule-associated protein 1B (MAP1B) gene, complete cds.	numan microtubule-associated protein 1B (MAP1B) gene, complete cds.	tuttian microhibule-associated protein 1B (MAP1B) gene, complete cds.	Munical micrombule-associated protein 1B (MAP1B) gene, complete cds.	WEINATE DEITHER OFFICE KINASE.	Timen interfacility of the Section o	luman bcl-2 mRNA	luman DNA sequence from clone CTA-833B7 on chromosome 22q12.3-13.2 Contains the ICF4 gene for cytosolic neutrophil factor 4 (40kD), the 5' part of the CSF2RB gene for	uman DNA sequence from class of the party of	cyclin tions CIA-83387 on chromosome 22q12.3-13.2 Contains the
<b>高能交通</b>	Ar 135298	AF133298	D00510	M21574	M21574	M21574	D87812	J02611	J03799	304046	L06237	222901	10001			$\neg \vdash$				AL008637 N	AL008637 H	
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4966	4966	5019		5165	5165	5165	2278	5287	5320	5324	5373	5375	5376	5377	5377	5517	5518	5564	5569	5716	-	
	CVD GG AG AA	A AF133298	A AF133298  A AF133298	LA AF133298  A AF133298  T D00510	A AF133298  T D00510  A M21574	A M21574  A M21574  A M21574	A AF133298  A AF133298  T D00510  A M21574  A M21574	A MZ1574  A MZ1574  A MZ1574  A MZ1574  A MZ1574  A MZ1574  A MZ1574	A A M21574  C J02611	A A M21574  A M21574	A AF133298  T D00510  A M21574  A M21574  A M21574  A D87812  T J02611  T J04046  T J04046	A AF133298  T D00510  A M21574  A M21574  A M21574  A D87812  T J02611  T J04046  E J06237	A AF133298  T D00510  A M21574  A M21574  A M21574  A M21574  A M21574  C J02611  J J04046  E J06237  L L06237  L L0	56         CVD         GG         AG         AA         AF133298           56         ADR         GG         AG         AA         AF133298           50         ADR         GG         AG         AA         AF133298           5         ADR         GG         AA         AF133298           5         ADR3         CC         AA         AF133298           5         ADR3         CC         AA         AA15574           6         ADR3         CC         AA         AA21574           7         ADR4         AC         AA         AA21574           8         ADR5         GG         AA         AA21574           9         ADR5         GG         AA         AA21574           1         VEFF         CC         CT         TT         J02611         I           1         VEFF         TT         CC         J04046         F           1         ADR5         GG         GT         TT         L06237         H           1         ADR5         AA         AT         TT         L06237         H	66         CVD         GG         AG         AA         AF133298           66         ADR         GG         AG         AA         AF133298           19         CVD         AA         AT         TT         D00510           55         ADR3         CC         AC         AA         M21574           55         ADR3         CC         AC         AA         M21574           55         ADR         CC         AA         M21574           5         ADR         CC         AA         M21574           6         ADR         AG         AA         M21574           7         VEFF         CC         AA         M21574           8         ADR5         GG         AA         M21574           9         CVD         AA         M21574           1         VEFF         TT         CC         J04046         F           1         ADR5         GG         GT         TT         L06237         H           ADR5         AA         AT         R         R         R         R         R           4DR5         CC         CT         TT         TT	66         CVD         GG         AG         AA         AF133298           66         ADR         GG         AG         AA         AF133298           19         CVD         AA         AT         TT         D00510           55         ADR3         CC         AC         AA         M21574           55         ADR3         CC         AA         M21574           55         ADR4         CC         AA         M21574           5         ADR5         CC         AA         M21574           6         ADR5         CC         AA         M21574           7         VEFF         CC         AA         M21574           8         ADR5         GG         AA         D87812           9         CVD         AA         M21574         D           1         VEFF         TT         CC         J04046         F           1         ADR5         GG         GG         TT         L06237         H           ADR5         AA         AT         CC         L06237         H           ADR5         TT         CC         L06237         H	M66         CVD         GG         AG         AA         AF133298           M66         ADR         GG         AG         AA         AF133298           M66         ADR         GG         AG         AA         AF133298           M66         ADR         GG         AG         AF133298           M67         ADR         AA         AF133298           M67         ADR         AA         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 CT         TT         L06237         B           9         ADR5         CC         CT         TT         L06237         B           9         ADR5         AA         AA         AA         AA         AA         AA         B           1         ADR         AA         A</td><td>966         CVD         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           919         CVD         AA         AT         TT         D00510           165         ADR3         CC         AC         AA         AF133298           65         ADR3         CC         AC         AA         AR13574           65         ADR3         CC         AC         AA         AR1574           65         ADR4         CC         AC         AA         AR1574           78         ADR5         CC         AA         AR21574         AR1574           80         ADR5         CC         AA         AR21574         AR1574           80         CC         CT         TT         L06237         B           80         ADR5         CC         TT         L06237         B           80         CC         CC         CC         L06237         B           80         CC         CC         CC         L06237         B</td><td>966         CVD         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           919         CVD         AA         AT         TT         D00510           165         ADR3         CC         AC         AA         M21574           65         ADR5         CC         AC         AA         M21574           65         ADR5         CC         AC         AA         M21574           66         ADR5         CC         AA         M21574         B           7         ADR5         GG         AA         M21574         B           87         VEFF         CC         AA         M21574         B           89         ADR5         GG         AA         M21574         B           80         CVD         AA         AA         M21574         B           81         ADR5         CC         CT         TT         L06237         B           82         ADR         AA         AA         AA         AA         <t< td=""><td>966         CVD         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           969         CVD         AA         AT         TT         D00510           165         ADR3         CC         AC         AA         M21574           65         ADR3         CC         AC         AA         M21574           65         ADR3         CC         AC         AA         M21574           66         ADR3         CC         AC         AA         M21574           67         ADR4         AG         AA         M21574           87         ADR5         CC         TT         T02611           80         CVD         AA         AA         D87312           81         ADR5         AC         CT         TT         L06237           82         ADR5         TT         CC         L06237           83         ADR5         TT         TT         M14784           84DR5         GG         GG         CC         AA<!--</td--></td></t<></td></t<>	M66         CVD         GG         AG         AA         AF133298           M66         ADR         GG         AG         AA         AF133298           M66         ADR         GG         AG         AA         AF133298           M67         ADR         GG         AA         AF133298           M69         AA         AT         TT         D00510           M60         ADR3         CC         AA         AA1574           M60         ADR4         AC         AA         AA1574           M60         ADR5         CC         AA         AA1574           M7         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  CT         TT         102611         B           8         ADR5         CC         CT         TT         L06237         B           9         ADR5         CC         CT         TT         L06237         B           9         ADR5         AA         AA         AA         AA         AA         AA         B           1         ADR         AA         A	966         CVD         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           919         CVD         AA         AT         TT         D00510           165         ADR3         CC         AC         AA         AF133298           65         ADR3         CC         AC         AA         AR13574           65         ADR3         CC         AC         AA         AR1574           65         ADR4         CC         AC         AA         AR1574           78         ADR5         CC         AA         AR21574         AR1574           80         ADR5         CC         AA         AR21574         AR1574           80         CC         CT         TT         L06237         B           80         ADR5         CC         TT         L06237         B           80         CC         CC         CC         L06237         B           80         CC         CC         CC         L06237         B	966         CVD         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           919         CVD         AA         AT         TT         D00510           165         ADR3         CC         AC         AA         M21574           65         ADR5         CC         AC         AA         M21574           65         ADR5         CC         AC         AA         M21574           66         ADR5         CC         AA         M21574         B           7         ADR5         GG         AA         M21574         B           87         VEFF         CC         AA         M21574         B           89         ADR5         GG         AA         M21574         B           80         CVD         AA         AA         M21574         B           81         ADR5         CC         CT         TT         L06237         B           82         ADR         AA         AA         AA         AA <t< td=""><td>966         CVD         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           966         ADR         GG         AG         AA         AF133298           969         CVD         AA         AT         TT         D00510           165         ADR3         CC         AC         AA         M21574           65         ADR3         CC         AC         AA         M21574           65         ADR3         CC         AC         AA         M21574           66         ADR3         CC         AC       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BAKEN	BASSING (SINE) CHINESIA (CHINESIA)		CHAREE	CalaMas	OF THE PROPERTY OF THE PROPERT	Discription of the cytosolic neutrophil factor 4 (40kD), the 5' part of the CSF2RB gene for granulocyte-macrophage low-affinity colony etimulating factor 2
27172	ADRS	99	AG	¥	AL008637	Human DNA sequence from clone CTA-833B7 on chromosome 22q12.3-13.2 Contains the NCF4 gene for cytosolic neutrophil factor 4 (40kD), the 5' part of the CSF2RB gene for granulocyte-macrophage low-affinity colony stimulating factor 2 recentor beta, EST3, STS
5717	CVD	00	AG	AA	AL008637	Human DNA sequence from clone CTA-833B7 on chromosome 22q12.3-13.2 Contains the NCF4 gene for cytosolic neutrophil factor 4 (40kD), the 5' part of the CSF2RB gene for granulocyte-macrophage low-affinity colony stimulatine factor 2 recentor hera BSTs. STS.
5850	CVD	99	AG.	¥¥	M95724	H. sapiens centromere autoantigen C (CENPC) mRNA, complete cds.
5959	CVD	99	AG	AA	U12789	Human clone HSH1 HMG CoA synthase mRNA, partial cds.
6151	ADR	ည	AC	ΑA	U49245	Human geranylgeranyl transferase type II beta-subunit mRNA, complete cds.
6236	ADR	Ħ	נל	<b>)</b>	NM_000436	Homo sapiens 3-oxoacid CoA transferase (OXCT), nuclear gene encoding mitochondrial protein, mRNA
6277	ADRS	TL	ĞŢ	99	NM_003477	Homo sapiens Pyruvate dehydrogenase complex, lipoyl-containing component X; E3-binding protein (PDX1), mRNA
6277	ADR	Ħ	GT	.00	NM_003477	Homo sapiens Pyruvate dehydrogenase complex, lipoyl-containing component X; E3. binding protein (PDX1), mRNA
6277	ADR3	Ħ	51	ÐÐ	NM_003477	Homo sapiens Pyruvate dehydrogenase complex, lipoyl-containing component X; E3-binding protein (PDX1), mRNA
6313	UEFF	သ	ರ	E	X05199	Human mRNA for plasminogen
6369	CVD	TT	ರ	ខ	X52011	H.sapiens MYF6 gene encoding a muscle determination factor
6374	ADR3	TT.	<u>م</u>	ន	X52022	H.sapiens RNA for type VI collagen alpha3 chain
6396	CVD	TT	ರ	႘	X54807	Human CYP2C8 gene for cytochrome P-450, 5' flank and exon 1
6486	CVD	ည	AG	AA	X69086	H.sapiens mRNA for utrophin
		•				

		r4			<b>7.</b>	۲4 .	14	4				Omplete comment	oupiele sequence.		, complete cds.	complete cds,	complete cds.	receptor) mRNA, complete cds.	complete cds,	complete cds.	lete sequence,	l ode	11 CUS.	Ar), member   }	1P), member 11	
	DESCRIPTION STATE OF THE PROPERTY OF THE PROPE	H.sapiens HNF4 mRNA for hepatocyte nuclear factor 4	H.sapiens HNF4 mRNA for hepatocyte nuclear factor A	H. Sapiens HNF4 mRNA for henatocute moles f	H.sapiens HNF4 mPNA for house	nière HNEA - PAYS (	tradplets filter filters for hepatocyte nuclear factor 4	clear factor	n.saptens mKNA for tyanodine receptor 2	H.Sapiens mRNA for ryanodine receptor 2	H.sapiens mRNA for ryanodine receptor 2	Homo sapiens BAC clone CTA-300C3 from 7031 2 Complete com-	Human mRNA for linomotein and II	an N. K. A Thomas	Himman Nr. V. A.T	The state of the s	numan na,k-A i Pase subunit alpha 2 (A TP1A2) gene, complete cds.	riuman endozepine (putative ligand of benzodiazepine receptor) mRNA, complete cds.	numan HLA-B-associated transcript 3 (BAT3) mRNA, complete cds.	numan HLA-B-associated transcript 3 (BAT3) nnRNA, complete cds.	Homo sapiens BAC clone CTB-60P12 from 7q21, complete sequence.	Homo sapiens caveolin gene, promoter region and marrial eds	ABCBI I: ATP-binding cassette only femily D A Con Z	II. ATP-hinding careette and to a careette	Homo sapiens ATP cassents hinding to a second of the secon	
			X76930 H.s	X76930 H.S.	X76930 H.s.	$\top$	1	T	T			AC002543 Hom	X00568 Hum	J05096 Hum	T	T	T			T		AF019742 Homo	AF091582 ABCB	AF091582 ABCB	AF165281 Homo	1 111111111
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BAYSN	6520	6520	6520	0200	6322	. 6522	6524	9659	9659	9659	6734	6763	0/43	7128	7128	7128	7363	7409	7409	8138	8168	+	$\dashv$			

HENGRIFFE DESCRIPTION SPECIFICATION OF THE PROPERTY OF THE PRO	Homo sapiens cytochrome P450 3A4 (CYP3A4) gene, promoter region.	Human peroxisome proliferator activated receptor gamma 2 mRNA, complete cds.	Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	Human microtubule-associated protein 1B (MAP1B) gene, complete cds.	Human microtubule-associated protein 1B (MAP1B) gene, complete cds.	Human microtubule-associated protein 1B (MAP1B) gene, complete cds.	Human pre-B cell stimulating factor homologue (SDF1b) mRNA, complete cds.	Human creatine kinase M mRNA, complete cds.	Homo sapieus lipoprotein lipase precursor, gene, partial cds.	Homo sapiens c-lbc mRNA for guanine nucleotide exchange factor Lbc, complete cds.	Homo sapiens c-lbc mRNA for guanine nucleotide exchange factor Lbc, complete cds.	Homo sapiens c-lbc mRNA for guanine nucleotide exchange factor Lbc, complete cds.	Homo sapiens A-kinase anchor protein (AKAP100) mRNA, complete cds.	Human CYP2C8 gene for cytochrome P-450, 5' flank and exon 1	Homo sapiens oxidase (cytochrome c) assembly 1-like (OXA1L), mRNA	Homo sapiens muscle glycogen phosphorylase (PYGM) mRNA, complete cds.	Homo sapiens muscle glycogen phosphorylase (PYGM) mRNA, complete cds.	Homo sapiens MSH55 gene, partial cds; and CLIC1, DDAH, G6b, G6c, G5b, G6d, G6e,	G6f, BAT5, G5b, CSK2B, BAT4, G4, Apo M, BAT3, BAT2, AIF-1, 1C7, LST-1, LTB,	TNF, and LTA genes, complete cds.
NOBE	AF185589	U63415	M21616	M21616	M21616	M21616	L06237	L06237	L06237	L36033	M14780	AF050163	AB055890	AB055890	AB055890	261710	X54807	NM_00501.5	AF066859	AF066859		AF129756	
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SINEGES	ADRS	CVD	ADR3	ADR	ADRS	ADR3	ADR	ADR3	ADRS	CVD	ADR3	ADR3	VEFF	ADRS	. UEFF	ADRS	CVD	ADR3	UEFF	VEFF		QAO .	
BAYSN	8249	8480	8577	8577	. 8577	8228	8653	8653	8653	8816	8931	8943	9243	9243	9243	9523	9940	10001	10541	10541		00901 -	

RENGBI ET DRSGRUFTIGNE ET STEETE STEE	D11456   Human mRNA for Xanthine debuderment	D11456 Ruman mRNA for Xanchine debud-	D11456 Himan mBNA 6. Varieties 2.		T		JUZO10 Human apolipoprotein B-100 mRNA, complete cds.	M10065 Human apolipoprotein E (epsilon-4 allele) gene. complete cde	M10065 Human apolipoprotein E (epsilon-4 allele) gene complete ode		 Human, intestinal fatty acid binding protein gene, complete cds and an Alu ranatidina		Human, intestinal fatty acid binding protein gene, complete cds, and an Alu renetitive	Human, intestinal fatty acid binding protein gene, complete cds, and an Alu repetitive		134424 Human acid alpha-glucosidase (GAA) mRNA complete cd.	1		T	34424 Human acid alpha-glucosidase (GAA) mRNA, complete cds.			$\top$	Transcriptions protein phosphatase 2C alpha 2 mRNA, complete cds.
NGB.	D1145	D1145	D1145	D5067	D&K47	7400	010701	M1006	M10065	M18079	M18070		M18079	M18079		M34424	M34424	M3dd2d		M34424	M34424	M60092	AF070670	
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No.XX	10745	10748	10749	10785	10811	10830	10070	10343	10949	10962	10962		10966	10966		11000	11000	11000	1001		10011	11020	11073	<u> </u> -

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11.92	ADRS	ŧ	AT	AA	NM 003477	Homo sapiens Pyruvate dehydrogenase complex, lipoyl-containing component X; E3-
						binding protein (PDX1), mRNA
11192	ADR3	Ţ	AT	AA	74PEOU MIN	Homo sapiens Pyruvate dehydrogenase complex, lipoyl-containing component X; E3-
		,		į		binding protein (PDX1), mRNA
11248	ADR3	သ	೮	T	X60435	H. sapiens gene PACAP for pitultary adenylate cyclase activating polypeptide
11248	ADR	႘	ರ	TI.	X60435	H.sapiens gene PACAP for pituitary adenylate cyclase activating polypeptide
11410	VEFF	99	GT	TI	AC004590	ABCC3: ATP-binding cassette, sub-family C (CFTR/MRP), member 3
11448	CVD	වල	AG	AA.	AF050163	Homo sapiens lipoprotein lipase precursor, gene, partial cds.
11448	ADR	99	AG	4A	AF050163	Homo sapiens lipoprotein lipase precursor, gene, partial cds.
11450	CYD	E	AT	*	AF050163	Homo sapiens lipoprotein lipase precursor, gene, partial cds.
11456	CVD	₹	AG	99	AF051427	Homo sapiens estrogen receptor beta mRNA, complete cds.
11462	CAD	99	GT	TI	AF051427	Homo sapiens estrogen receptor beta mRNA, complete cds.
11483	ADRS	Ħ	ಚ	8	L19592	Homo sapiens interleukin 8 receptor alpha (IL8RA) gene, complete eds.
11483	ADR3	E	t)	ઇ	L19592	Homo sapiens interleukin 8 receptor alpha (IL8RA) gene, complete cds.
11483	ADR	ŢŢ	೮	8	L19592	Homo sapiens interleukin 8 receptor alpha (IL8RA) gene, complete cds.
11531	CVD	gg	AG	AA	X52773	Human mRNA for retinoic acid receptor-like protein
						Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the
11536	CAS	 ဗ	. g	99	AI 022721	alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal
				:		Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome
						Proliferato
						Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the
11537	ADR	<b>{</b>	AG ·	S.	AL022721	alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal
			-			Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisonne
					7	

DESCRIPTION	Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	Homo sapiens acyl-CoA synthetase 4 (ACS4) mRNA, complete cds.	Homo sapieus cytosolic phospholipase A2-gamma mRNA, complete cds.	Homo sapiens cytosolic phospholipase A2-gamma mRNA, complete cds.	Homo sapiens thrombin-activable fibrinolysis inhibitor gene, 5'-flanking region.	Homo sapiens thrombin-activable fibrinolysis inhibitor gene, 5'-flauking region.	Homo sapiens thrombin-activable fibrinolysis inhibitor gene, 5'-flanking region.	Homo sapiens thrombin-activable fibrinolysis inhibitor gene, 5'-flanking region.	Homo sapiens thrombin-activable fibrinolysis inhibitor gene, 5'-slanking region.	Homo sapiens chromosome 14q24,3 clone BAC270M14 transforming growth factor-beta 3 (TGF-beta 3) gene, complete cds; and unknown cenes	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the	alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal	Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome	Proliferator delta	Human DNA sequence from clone 109F14 on chromosome 6n21.2-213. Contains the
PE22 WASE GOVERNORS	AB043943 Hom	AB043943 Hom	AF030555 Hom	AF058921 Hom	AF058921 Hom	AF080222 Hom	AF080222 Hom	AF080222. Home	AF080222 Homo	AF080222 Home	AF107835 (TGF.	AF091582 ABCE	AF091582 ABCE	AF091582 ABCE	AF091582 ABCE	AF091582 ABCB	AF091582 ABCB	Huma	Al.02271		Prolife	AL022721 Human
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SNP class	ADR3	ADRS	ADR3	ADR3	ADRS	ADRS	ADR3	ADR	ADRS	UEFF	ADR	ADR3	ADRS	ADR	UBFF	ADR	VEFF		ADRS			ADR
BAYAN	11727	11728	11914	11938	11938	11950	11950	11950	11951	11951	12008	12031	12031	12031	12032	12032	12032		12148			12148

A THE REPORT OF THE PROPERTY O	alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal	Protein RPL 10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome	Proliferator della	Human DNA sequence from clone 109F14 on chromosome 6p21,2-21,3. Contains the	alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal	Proliferator delta	D11456 Human mRNA for Xanthine dehydrogenses complete of	D11456 Human mRNA for Xanthine debudences	D11456 Human mBNA for Vantage 1.1.	T		T	D86982 Human mRNA for KIAA0229 gene, partial cds.	HSVDACIX Human voltage-dependent anion channel isoform 1 (VDAC) mRNA commissioned	HSVDACIX Human voltage-dependent anion channel isoform 1 (VDAC) mBNA completed.	M33336 Hurnan cAMP-dependent protein kinase twee Lalpha submit (PDF & D14) DNA	M33336 Human cAMP-dependent protein kinase tyne Lainha suhmit (PRK & B.14)	M85168 Human glycogen debranching enzyme mRNA complete eds	M85168 Human glycogen debranchine enzyme mRNA complete ode	U12789 Human clone HSH1 HMG CoA synthese mRNA martial cde	U12789 Human clone HSH1 HMG CoA synthese mRNA mariel cdc	U12789 Human clone HSH1 HMG CoA synllase mRNA marriel cds	U12789 Human clone HSH1 HMG CoA synthage mRNA merriel cdc
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nuclear	AF044954	<b>8</b>	ย	ш	EFF
sapiens NADH:ubiquinone oxidoreductase PGIV subunit mRNA, nuclear ig mitochondrial protein, complete cds.	ĀF044953	8	ದ	Ħ	ADR
Homo sapiens PAC clone RP5-1131G17 from 7p15.1-p14, complete sequence.	AC006022	TT	CT	ည	EFF
Homo sapiens kallistatin (PI4) gene, exons 1-4, complete cds.	L28101	AA	AG	GG	ADRS
H.sapiens mRNA for glycerol kinase testis specific 1.	HSGKTS1	ខ	t3	TT	ADR
H. sapiens mRNA for glycerol kinase testis specific 1.	HSGKTS1	ප	ಚ	TT	ADR3
Homo sapiens ccr2b (ccr2), ccr2a (ccr2), ccr5 (ccr5) and ccr6 (ccr6) genes, complete cand lactoferrin (lactoferrin) gene, partial cds, complete sequence.	U95626	γγ	AG	8	UEPF
Human Xq28 mRNA, complete cds.	U46023	ΨΨ	. AC	ខ	VEFF
Human Xq28 mRNA, complete cds.	U46023	í	AG	CG	CVD
Human Xq28 mRNA, complete cds.	U46023	¥¥	AG	OD	ADR
Human Xq28 mRNA, complete cds.	U46023	A.A	AG	99	VEFF
Human Xq28 mRNA, complete cds.	U46023	AA	AG	99	UEFF
Human clone HSH1 HMG CoA synthase mRNA, partial cds.	U12789	AA	AG	99	ADRS
Human clone HSH1 HMG CoA synthase mRNA, partial cds.	U12789	AA .	AG	ည	ADR3
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ORDA ETANOBIE TO DOS OR BATON PAR SE CONTACTOR OF THE ACTION OF THE ACTI	Homo sapiens NADH-ubiquinone oxidoreductase 42 kDa subumit mRNA, complete cds, nuclear gene encoding mitochondrial protein.	Homo sapiens NADH-ubiquinone oxidoreduciase 42 kDa subunit mRNA, complete cds, nuclear gene encoding mitochondrial protein.	Homo sapiens NADH-ubiquinone oxidoreductase 42 kDa subunit mRNA, complete cds, nuclear gene encoding mitochondrial protein.	Homo sapiens, Rab geranylgeranyltransferase, alpha subunit, clone MGC:1485	Homo sapiens pyruvate dehydrogenses (linomido) 11.1. 2 mays 10.	Homo sapiens partial ZNF202 gene for zinc fineer motein homolog.	Homo sapiens partial ZNF202 gene for zinc finger motein homolog.	Human 2,3-oxidosqualene-fanosterol curlase mDNA	Hunan arvlaceramide descetaises month	Forman arujacemmide descention Date	insplutaminase 2 (C notinesses).	Homo saniens linearate in linear account to the contract of th	Human mRNA for lanceterni cuntance constitutions.	Human mRNA for lancefern complete cos.	Human Ivsosomal acid linesethology	Human lysosomal acid linase/chylesteryl ashares mkly.	NDUFVI=NADH:ubiquinone oxidoreduciase flavoprotein I subunit (human, kidney,	Homo sapiens beroxisome proliferative askingto	Free Processing Internative activated receptor, alpha (PPARA), mRNA.
	AF087661	AF087661	AF087661	BC003093	NM_005390	AJ276178	AJ276178	U22526	L32179 E	L32179 H	AL031651 tr	AF050163 H	D63807 H	D63807 H	M74775 H	M74775 Hi	S67973	XM_010049 Ho	- I
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	e eriei berren in.	TANK CALL MEET	il i	S. C. C. Library in Fig.	時期ではない。	Human DNA sequence from clone CITF22-45C1 on chromosome 22 Contains the 3' part of
38559	c <sub>S</sub>	ខ	AC	¥	AL133392	the CSF2RB gene for low-affinity granulocyte-macrophage colony stimulating factor 2
	·					receptor beta, the CSF2RB2 gene for colony stimulating factor 2 receptor beta 2, ESTs, STS
						Human DNA sequence from clone CITF22-45C1 on chromosome 22 Contains the 3' part of
38959	EFF	ප	AC	¥	AL133392	the CSF2RB gene for low-affinity granulocyte-macrophage colony stimulating factor 2
		•		-		receptor beta, the CSF2RB2 gene for colony stimulating factor 2 receptor beta 2, ESTs, STS
39292	ADRS	99	AG	¥¥	M33388	Human cytochrome P450 IID6 (CYP2D6) gene, complete cds.
39698	· ADR3	TI	ಭ	8	81920X	Human mRNA for cytochrome P450 db1 variant b
39756	ADR3	ŢŢ	ರ	ည	X58468	Human CYP2D7BP pseudogene for cytochrome P450 2D6
39951	ADR	E	5	ည	AF005896	Homo sapiens Na K-ATPase beta-3 subunit (atp1b3) gene, exon 7 and complete cds.
39951	ADRS	F	ឧ	8	AF005896	Homo sapiens Na K-ATPase beta-3 subunit (ap1b3) gene, exon 7 and complete cds.
40466	EFF	99	15	TT	AB043821	Homo sapiens GPVI mRNA for platelet glycoprotein VI-3, complete cds.
40466	UEFF	99	7.5	11.	AB043821	Homo sapiens GPVI mRNA for platelet glycoprotein VI-3, complete cds.
40466	VEFF	GĠ	GT	TT	AB043821	Homo sapiens GPVI mRNA for platelet glycoprotein VI-3, complete cds.
44442	ADRS	AÄ	AG	99	NM_001931	Homo sapiens dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex) (DLAT), mRNA
25504	an a	Ę	Ę		SECONDARY:	SECONDARY TO Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase
Torre	į	•		3	161000 NN	(hydroxymethylglutaricaciduria) (HMGCL), mRNA
67535	auv	٤	Ç	3	SECONDARY:	SECONDARY TO Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase
25000	WOW.	}	2	٤	NM_000191	(bydroxymethylglutaricaciduria) (HMGCL), mRNA
02955	VERF	رر	£	<u>.</u>	SECONDARY:	SECONDARY TO Homo sapiens carnitine palmitoyltransferase I, liver (CPT1A), nuclear
		}	;	•	NM_001876	gene encoding mitochondrial protein, mRNA
55736	ADRS	AA	AG -	ĐĐ	SECONDARY: M23234	SECONDARY TO ABCB4

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RESOLUTION OF STATE OF THE STAT	SECONDARY TO ABCB4	SECONDARY TO Human 52-kD ribonucleoprotein Ro/SSA mRNA, complete cds.	SECONDARY TO Human 52-kD ribonucleoprotein Ro/SSA nuRNA, complete cds.	SECONDARY TO Human 52-kD ribonucleoprotein Ro/SSA mRNA, complete cds.	SECONDARY TO Human 52-kD ribonucleoprotein Ro/SSA mRNA, complete cds.	SECONDARY TO H.sapiens centromere autoantigen C (CENPC) mRNA, complete eds.	SECONDARY TO H.sapiens centromere autoantigen C (CENPC) mRNA, complete cds.	SECONDARY TO H. sapiens centromere autoantigen C (CENPC) mRNA, complete cds.	SECONDARY TO H. sapiens centromere autoantigen C (CENPC) nıRNA, complete cds.	SECONDARY TO Homo sapieus COX10 homolog, cytochrome c oxidase assembly protein, heme A: farnesyltransferase (yeast) (COX10), nuclear gene encoding mitochondrial protein, mRNA	SECONDARY TO Homo sapieus COX10 homolog, cytochrome c oxidase assembly protein, heme A: famesyltransferase (yeast) (COX10), miclear gene encoding mitochondrial protein, mRNA	
ALIE NCBL	SECONDARY: M23234	SECONDARY: M34551	SECONDARY: M34551	SECONDARY: M34551	SECONDARY: M345511	SECONDARY: M95724.	SECONDARY: M95724	SECONDARY: M95724	SECONDARY: M95724	SECONDARY: NM_001303	SECONDARY: NM_001303 P	
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<b>BAYSIN</b>	55748	55813	55845	55845	55845	55923	55923	55945	55945	26007	56007	

FARDON STATES OF	SECONDARY: SECONDARY TO Homo sapiens, ATPase, Na+/K+ transporting, beta 1 polypeptide	3.	CC AF066859 complete cds.	SECONDARY: SECONDARY TO Homo sapiens muscle glycogen phosphorylase (PYGM) mRNA, AF066859 complete cds.	SECONDARY: SECONDARY TO Human mRNA for Xanthine debydrogenase, complete cds.	T SECONDARY: SECONDARY TO Human mRNA for Xanthine dehydrogenase, complete cds.	SECONDARY: D11456	SECONDARY: SECONDARY TO Human mRNA for Xanthine dehydrogenase, complete cds.	SECONDARY: SECONDARY TO Homo sapiens TSC2, NTHL I/NTH1 and SLC9A3R2/E3KARP genes, AB014460 partial and complete cds.	SECONDARY TO Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3, SECONDARY: Contains the alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S AL022721 Ribosomal Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome Publiferator delta	SECONDARY:
	SECONDARY: BC00006	SECONDARY: AF066859	SECONDARY: AF066859	SECONDARY: AF066859	SECONDARY: D11456	SECONDARY: D11456	SECONDARY: D11456	SECONDARY: D11456		SECONDARY: Col AL022721 Rib Per	SECONDARY: SEC
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	26780	56876	56876	56876	86978		57000	57000	57313	57734	57837

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AB043943	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial eds.	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	SECONDARY TO H.sapiens mRNA for 3-hydroxy-3-methylglutaryl coenzyme A synthase		SECONDARY TO Human Xq28 niRNA, complete cds.	SECONDARY TO Human Xq28 mRNA, complete cds.		SECONDARY TO Homo sapiens putative N6-DNA-methyltransferase (N6AMTI), mRNA
AB043943	SECONDARY: AB043943	SECONDARY: AB043943	SECONDARY: AB043943	SECONDARY: AB043943	SECONDARY: AB043943	SECONDARY: AB043943	SECONDARY: X83618	SECONDARY: U46023	SECONDARY: U46023	SECONDARY: U46023	SECONDARY: U46023	SECONDARY:
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RECENTATION OF THE PROPERTY ON THE PROPERTY OF		SECONDARY TO Homo sapiens pulative N6-DNA-methyltransferase (N6AMT1), mRNA		SECONDARY TO Homo sapiens putative N6-DNA-methyltransferase (N6AMT1), mRNA	SECONDARY TO Homo sapiens putative N6-DNA-methyltransferase (N6AMT1), mRNA	SECONDARY TO Homo sapiens putative N6-DNA-methyltransferase (N6AMTI), mRNA	SECONDARY. TO Homo. sapiens putative. N6_DNA-methyltransferase (N6AMT1), mRNA	SECONDARY TO Homo sapiens, NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (14kD, B14), clone MGC:3686 IMAGE:3619356 mRNA complete 245	SECONDARY TO Homo sapiens, NADH dehydrogenase (ubiquinone) Talpha subcomplex, 6 (14kD, B14), clone MGC 3686 IMAGE 3619356 mRNA complex.	SECONDARY: SECONDARY TO Homo sapiens, NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, BC002772 6 (14kD, B14), clone MGC.3686 IMAGE.3619356 mBNA complexes.	SECONDARY TO nuclear hormone receptor PRR2	SECONDARY TO nuclear hormone receptor PRR2	SECONDARY: SECONDARY TO nuclear hormone recentor PRR2	7777 7 7017
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58886	ADR3	**	AG	9	SECONDARY:	22q12.3-13.2 Contains the NCF4 gene for cytosolic neutrophil factor 4 (40kD), the 5' part
			?	3	AL008637	of the CSF2RB gene for granulocyte-macrophage low-affinity colony stimulating factor 2
			•			receptor beta
					-	SECONDARY TO Human DNA sequence from clone CIA-833B7 on chromosome
70003	700.4		Ç	(	SECONDARY:	22q12.3-13.2 Contains the NCF4 gene for cytosolic neutrophil factor 4 (40kD), the 5' part
00000	Que la company de la company d	<b>§</b>	2	3	AL008637	of the CSF2RB gene for granulocyte-macrophage low-affinity colony stimulating factor 2
			<u></u>	-		receptor beta
28926	ADR3	20	5	- ; - L	SECONDARY: L78810	SECONDARY TO Home sapiens ADP/ATP carrier protein (ANT.2) gene, complete cds.
58926	ADRS	8	. ຊ	E	SECONDARY: L78810	SECONDARY TO Homo sapieus ADP/ATP carrier protein (ANT-2) gene, complete cds.
58926	CVD	8	៦	E	SECONDARY: L78810	SECONDARY TO Homo sapiens ADP/ATP carrier protein (ANT-2) gene, complete cds.
89685	ADRS	V V	AG	· B	SECONDARY: L78810	SECONDARY TO Honto sapiens ADP/ATP carrier protein (ANT-2) gene, complete cds.
58968	ADR3	AA	AG	99	SECONDARY: L78810	SECONDARY TO Homo sapiens ADP/ATP carrier protein (ANT-2) gene, complete cds.
. 58985	ADRS	ဌ	AG	₹	SECONDARY: L78810	SECONDARY TO Homo sapiens ADP/ATP carrier protein (ANT-2) gene, complete cds.
59113	ADR5	ន	8	S 99 .	SECONDARY:	SECONDARY: SECONDARY TO Homo sapiens acyl-CoA synthetase 4 (ACS4) mRNA, complete cds.

sepiens lanosterol synthase (2,3-oxidosqualene-lanosterol sapiens lanosterol synthase (2,3-oxidosqualene-lanosterol lanosterol synthase (2,3-oxido
ARY: SECONDARY TO Homo sap S55  4RY: SECONDARY TO Homo S40 cyclase) (LSS), mRNA RY: SECONDARY TO Homo S40 cyclase) (LSS), mRNA RY: SECONDARY TO Homo sapic SY: SECONDARY TO Homo sapic
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59236 59237 59237 59237 59363 59363 59363

DESCRIPTION CONTRACTOR OF THE PROPERTY OF THE	SECONDARY TO Homo sapiens transcription factor IID mRNA, complete cds.	SECONDARY TO Human glycogen debranching enzyme isoform I (AGL) mRNA,	alternatively spliced isoform, complete cds.	Homo sapiens putative N6-DNA-methyltransferase (N6AMTI), mRNA	Homo sapiens putative NG-DNA-methyltransferase (N6AMT1), mRNA	nuclear hormone receptor PRR2	nuclear hormone receptor PRR2	nuclear hornone receptor PRR2	nuclear hormone receptor PRR2	Homo sapiens lipoprotein lipase precursor, gene, partial cds.	MTM1: myotubular myopathy 1	MTM1: myotubular myopathy 1.	MTM1. myotubular myopathy 1	MTM1: myotubular myopathy 1	MTMR2: myotubularin related protein 2	MTMR2: myotubularin related protein 2	MTMR2; myotubularin related protein 2	SLC24A3: solute carrier family 24 (sodium/potassium/calcium exchanget), member 3	Selenoprotein P genomic region	Selenoprotein P genomic region	Selenoprotein P genomic region
M34960	SECONDARY: M34960	SECONDARY:	U84007	NM_013240	NM_013240	NM_003889	NM_003889	NM_003889	NM_003889	AF050163	U46024	U46024	U46024	U46024	US8033	U58033	U58033	AF169257	AC008945	AC008945	AC008945
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AC008945 Selenoprotein P genomic region G62788 SHGC-140326 Human Homo sapiens STS genomic, sequence tagged site. AF101918 Human Homo sapiens genomic clone pTWB28.01, DNA sequence. NM_016347 N-Accetyltransferase Camello 2 NM_016347 N-Accetyltransferase Camello 2 NM_016347 N-Accetyltransferase Camello 2 AK055126 HS cDNA FLJ3054 fis AJ27891 Homo sapiens partial mRNA; ID ED166-4A2 SECONDARY: SECONDARY: SECONDARY TO Homo sapiens mRNA for Cdc42-interacting protein 4 (CIP4) CONDARY: SECONDARY:	SECONDARY TO Homo sapiens mRNA for Cdc42-interacting protein 4 (CIP4)	SECONDARY TO Home sapiens mRNA for Cdc42-interacting protein 4 (CIP4)
AC008945 ACONDARY:		SECONDARY: S
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## Table 4 Cohorts

Given are names (as used in table 5) and formations of the various cohorts that were used for genotyping

COHORT	i December
	Definition
HELD_ALL_GOOD/BAD	Healthy elderly individuals of both genders with good or bad serum lipid profiles (as defined in table 1a)
HELD_FEM_GOOD/BAD	Healthy elderly individuals (female) with good or bad serum lipid profiles (as defined in table la)
HELD_MAL_GOOD/BAD	Healthy elderly individuals (male) with good or bad serum lipid profiles (as defined in table la)
CVD_ALL_CASE/CTRL	Individuals with diagnosis of cardiovascular disease and healthy controls (both genders)
CVD_FEM_CASE/CTRL	Individuals with idiagnosis of cardiovascular disease and healthy controls (female)
CVD_MAL_CASE/CTRL	Individuals with diagnosis of cardiovascular disease and healthy controls (male)
HELD_FEM_ADRCTRL	Female individuals that tolerate adminstration of cerivastatin without exhibiting signs of ADR (as defined in table 1b)
HELD_FEM_ADRCASE	Female individuals that exhibited ADR (as defined in table 1b) upon administration of cerivastatin
HELD_MAL_ADRCTRL	Male individuals that tolerate adminstration of cerivastatin without exhibiting signs of ADR (as defined in table 1b)
HELD_MAL_ADRCASE	Male individuals that exhibited ADR (as defined in table 1b) upon administration of cerivastatin
HELD_ALL_ADRCTRL	Individuals of both genders that tolerate adminstration of cerivastatin without exhibiting signs of ADR (as defined in table 1b)
HELD_ALL_ADRCASE	Individuals of both genders that exhibited ADR (as defined in table 1b) upon administration of cerivastatin
HELD_FEM_LORESP	Female individuals with a minor response to cerivastatin administration (as defined in table 1b)
HELD_FEM_HIRESP	Female individuals with a high response to to cerivastatin administration (as defined in table 1b)
HELD_FEM_HIHDL/LOHDL	[ Healthy elderly individuals (female) with high or low
HELD_MAL_HIHDL/LOHDL	serum HDL cholesterol levels (as defined in table 1c) Healthy elderly individuals (male) with high or low serum HDL cholesterol levels (as defined in table 1c)
HELD_ALL_HIHDL/LOHDL	Healthy elderly individuals of both genders with high or low serum HDL cholesterol levels (as defined in table 1c)
HELD_FEM_ADR3CASE	Female individuals that exhibited advanced ADR (as defined in table 16) upon administration of cerivastatin
	administration of certivastatin

COHORT	Definition
HELD_MAL_ADR3CASE	Male individuals that exhibited advanced ADR (as defined in table 1b) upon administration of cerivastatin
HELD_ALL_ADR3CASE	Individuals of both genders that exhibited advanced ADR (as defined in table 1b) upon administration of cerivastatin
HELD_FEM_VLORESP	Female individuals with a very low response to cerivastatin administration (as defined in table 1b)
HELD_FEM_VHIRESP	Female individuals with a very high response to cerivastatin administration (as defined in table 1b)
HELD_FEM_ADR5CASE	Female individuals that exhibited severe ADR (as defined in table 16) upon administration of cerivastatin
HELD_MAL_ADR5CASE	Male individuals that exhibited severe ADR (as defined in table 1b) upon administration of certivastatin
HELD_ALL_ADR5CASE	Individuals of both genders that exhibited severe ADR (as defined in table 1b) upon administration of cerivastatin
HELD_FEM_ULORESP	Female individuals with a ultra low response to cerivastatin administration (as defined in table 1b)
HELD_FEM_UHTRESP	Female individuals with a ultra high response to to cerivastatin administration (as defined in table 1b)

Table Sa and Sb Cohort sizes and p-values of PA SNPs

The baySNP number refers to an internal numbering of the PA SNPs. Cpval denotes the classical Pearson chi-squared test, Xpval denotes the exact version of Pearson's chi-squared test, LRpval denotes the likelihood-ratio chi-squared test.. Cpvalue, Xpvalue, and LRpvalue are Interscience 1993), and (A. Agresti, Statistical Science 7, 131 (1992)). The GTYPE and Allele p values were obtained through the respective calculated as described in (SAS/STAT User's Guide of the SAS OnlineDoc, Version 8), (L. D. Fisher and G. van Belle, Biostatistics, Wiley chi square tests when comparing COHORTs A and B. For GTYPE p value the number of patients in cohort A carrying genotypes 11, 12 or 22 (FQ11 A, FQ 12 A, FQ 22 A; genotypes as defined in table 3) were compared with the respective patients in cohort B (FQ11 B, FQ 12 B, FQ 22 B; genotypes as defined in table 3) resulting in the respective chi square test with a 3x2 matrix. For Allele p values we compared the allele count of alleles 1 and 2 (A1 and A2) in cohorts A and B, respectively (chi square test with a 2×2 matrix). SIZE A and B: Number of patients in cohorts A and B, respectively. See table 4 for definition of COHORTs A and B.

Table 5a Cohort sizes and frequency of alleles and genotypes

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SRT B	HELD_FEM_LORESP	HELD_FEM_ADRCTRL	CVD_FEM_CTRL	HELD ALL ADRCTRL	CVD_FEM_CTRL	HBLD_ALL_ADRCTRL	HELD_FEM_ADRCTRL	HELD FEM CTRL	HELD MAL ADRCTRE	HELD ALL ADRCTRI		MELD_FEM_ADRCIRE	HELD_MAL_GOOD	HELD_FEM_GOOD	HELD FEM ADRCTRI	CTRL	CTRI	į	된	HELD_FEM_LORESP	HELD_FEM_LORESP	CIRC	HELD PEM ADPORTOR	DRCIR
COH	LD FE	D FEM	YS FE	DALL	图图	D ALL	FEM	ED EB	MAL	ALL		rcm	D MA	D FEN	FEM	CVD FEM CTRL	CVD ALL CTRI	בפאל	CYD_FEW_CIRC	FEM	FEM	CVD MAL CTRE	PFM A	ζ,   13.
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		HELD_ALL_ADRCASESULN	HELD_MAL_ADRCASESULN	HELD FEM ADROASEGUES	STOCK.	SESULN	SEJULN	SESINN		25	ESULN		E SOLEN	ESULN	BULN		es Se	BULN	SE		SULN	1
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9		JALL.	LD MAL	LD FEW		HELD_FEM_ADRCASESULN	HELD_FEM_ADRCASESULN	HELD MAL ADRCASESINN		HELD_FEM_HIRESP	HELD_ALL_ADRCASESULN	HELD All ADDOVERS		HELD_FEM_ADRCASESULN	HELD_MAL_ADRCASESULN	1	neto_rem_ADRCASE	HELD FEM_ADRCASESULN	HELD ALL ADRCASE		HELD_MAL_ADRCASESULN	
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## Table 5b p-values of PA SNPs

A SNP is considered as associated to cardiovascular disease, adverse statin response or to efficacy of statin treatment, respectively, when one of the p values is equal or below 0.05.

29 29				CTYPE		ALLELE	ALLELI
	THE RESERVED BY THE PARTY OF TH	<b>PPVA</b>		ERPVAI	CPVAL	<b>建制的企业进行。</b> "由于	LRPVAL
20	HELD_FEM_LIP	0,0996			0,0441	0,0533	0,0438
	HELD_ALL_ADR3ULN	0,0483	0,0484	0,0493	0,1053	0,1185	0,1048
29	HELD_ALL_LIP	0,0912	0,0952	0,091	0,0503	0,0625	0,05
52 .	HELD_ALL_CC	0,0112	0,0128	0,0099	0,0015	0,0023	0,0014
52	HELD_MAL_HDL	0,0237	0,0238	0,0194	0,8213	0,8292	0,8214
52	HELD_FEM_CC	0,0818	0,0956	0,08	0,0293	0,0436	0,0282
52	HELD_MAL_CC	0,1499	0,2053	0,1393	0,0303	0,0547	0,0298
52	HELD_MAL_LIP2	0,1121	0,1133	0,1112	0,0423	0,0429	0,0422
57	HELD_FEM_CC	0,0168	0,008	0,0108	0,0076	0,0106	0,0049
118	HELD_MAL_LIP2	0,1081	0,1089	0,1043	0,0466	0,0501	0,0462
137	HELD_MAL_ADRSULN	0,0575	0,0872	0,0156	0,0892	0,1027	0,0951
137	HELD_ALL_ADR5ULN	0,0307	0,0274	0,0218	0,2446	0,2504	0,2486
137	HELD_ALL_ADR3ULN	0,034	0,035	0,0255	0,0671	0,0747	0,0686
179	HELD_MAL_ADR5ULN	0,0094	0,0241	0,0154	0,9216	1	0,921
179	HELD_MAL_ADR3ULN	0,0452	0,0479	0,0408	0,5445	0,7636	0,5327
179	HELD_ALL_ADR5ULN	0,0415	0,0537	0,0756	0,7311	0,8135	0,7272
179	HELD_ALL_ADR	0,0691	0,0447	0,0464	0,2487	0,3013	0,2482
240	HELD_ALL_ADR3ULN	0,1154	0,1318	0,0756	0,04	0,0539	0,0281
240	HELD_MAL_ADR3ULN	0,0641	0,0976	0,0399	0,0835	0,1215	0,0507
241	HELD_ALL_ADR3ULN	0,0987	0,0984	0,1033	0,0237		0,0262
241	HELD_ALL_ADR5ULN	0,1495	0,1519	0,1611	0,04	0,0527	0,0464
	HELD_MAL_ADR3ULN	0,1757	0,2127	0,1775	0,0411	0,055	0,0459
288	CVD_ALL	0,1013	0,1098	0,0863	0,0462	0,0557	0,0439
384	CVD_ALL	0,0214	0,022	0,0205	0,1828	0,1946	0,1831
384	HELD_FEM_CC	0,0793	0,0887	0,0704	0,0214	0,0299	
533			0,0932	0,0905	0,0387	0,0299	0,021
542	HELD_FEM_ADR	0,0522	0,0292	0,0417	0,0922	0,1056	0,0359

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Designation of	Adall Contestant Assessed			•	•		
BAYSR	P SECONDARISON	GIV	E CAVE	E (GIVP	ATTEL	ALLER	14301 4500 450 450 450 450
. 576	HELD ALL LIP				2 1	XPVAY	ERPVAI
576	HELD_FEM_LIP	0,034				0,0641	0,012
608	· CVD_MAL	. 0,0403			0,0416	0,0583	0,017
614	· HELD_MAL_HDL	0,003			0,0027	0,0035	0,0035
614		0,0069				0,0001	0
614	HELD_ALL_CC	0,0045		0,0031	0,0052	0,008	0,0047
614	HELD_MAL_CC	0,0694		0,0689	0,0102	0,0154	0,0101
	HELD_MAL_LIP	0,1792	0,254	0,1858	0,0113	0,0153	0,0123
614	CVD_ALL	0,1654	0,1652	0,1594	0,0202	0,0237	0,0188
614	HELD_FEM_CC	0,031	0,0198	0,0239	0,0446	0,0537	0,0387
738	CVD_ALL	0,0999	0,1019	0,0962	0,0261	0,0303	0,0257
1056	HELD_ALL_HDL	0,1007	0,1082	0,0989	0,0323	0,0468	0,0304
1056	HELD_FEM_LIP	0,0488	0,0518	0,0403	0,0695	0,09	0,0691
1092	HELD_MAL_ADRSULN	0,0404	0,0443	0,0114	0,6514	0,7766	0,6465
1524	HELD_MAL_CC2	0,0122	0,0142	0,0107	0,0079	0,0113	<b></b>
1524	HELD_ALL_LIP	0,0507	0,0381	0,0237	0,0592	0,0717	0,0062
1524	HELD_ALL_CC	0,0681	0,0671	0,0561	0,025	0,0717	0,0581
1574	CVD_MAL	0,0611	0,0678	0,0422	0,3189	<u>                                     </u>	0,0248
1582	HELD_MAL_ADR3ULN	0,1522	0,1512	0,0956	-	0,4133	0,3254
1657	HELD_FEM_EFF	0,05	0,0604	0,047	0,0468	0,0648	0,0295
1722	CVD_MAL	0,013	0,0128		0,4599	0,5588	0,459
1756	HELD_MAL_ADRSULN		0,0857	0,0135	0,3717	0,4376	0,3729
1757	HELD_ALL_CC	0,02		0,1003	0,0402	0,063	0,068
1757	HELD_FEM_CC	0,0517	0,0205	0,0053	0,3618	0,386	0,3603
1757	HELD_FEM_VEFF		0,0569	0,015	0,1242	0,1342	0,1193
1757	HELD_MAL_ADR	0,1217	0,1247	0,1208	0,0423	0,0505	0,0422
1765	HELD_ALL_LIP	0,0536	0,05	0,0501	0,6703	0,7693	0,6702
1767		0,0466	0,0494	0,0442	0,3068	0,3533	0,3058
1767	HELD_ALL_ADR3ULN	0,0082	0,0075	0,0036	0,0053	0,0066	0,0026
	HELD_ALL_ADRSULN	0,0608	0,0467	.0,0302	0,0196	0,0231	0,0086
	HELD_MAL_ADRSULN	0,183	0,216	0,0679	0,075	0,1229	0,0194
1767	HELD_FEM_ADR3ULN	0,0371	0,0348	0,0221	0,0341	0,0408	0,0251
		0,1692	0,1875	_0,1061	0,0606	_0,0741	-0,0334-
1837	HELD_ALL_ADR3ULN	0,0408	0,0398	0,0402	0,0225	0,0282	0,0196
_						3,0202	0,0196

	P COMPARISON	GIV	PELCTY	E GIYP	E ABEEI	EATTE	E ALLELE
		CPV	XI Xev	E LRPV	u eva	XPVA	(1年2月1日) (1月1日) こんんこうりょう
1837	HELD_FEM_LIP	0,033	THE APPLICATION OF THE PERSON	WATER CATHER S	<b>企業的學習的意思</b>	Carl Section 1	140 Part 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
1837	HELD_ALL_LIP	0,046	6 0,046				-,
1837	HELD_ALL_ADR	0,05	2 0,048				
1854	HELD_FEM_LIP	0,051	2 0,052	_	0,0661		0,0708
1862	HELD_FEM_LIP	0,056	2 0,058		i	0,0264	0,0658
2085	HELD_FEM_CC	0,014	9 0,0109	0,0118		0,0096	0,0229
2085	HELD_ALL_CC	0,038	8. 0,038	0,0345	[	0,02	0,0081
2093	HELD_MAL_CC	0,047	0,0249		0,0015	0,002	0,0183
2093	HELD_ALL_CC	0,159	5 0,1532	_1		0,0501	0,0013
2109	HELD_MAL_HDL	0,0044	0,0028		0,0341	0,0543	0,0383
2109	HELD_ALL_HDL	0,0187	0,0127		0,059	0,065	0,0299
2109	HELD_ALL_LIP2	0,0438	0,0439	_1	0,015	0,0152	0,0546
2109	HELD_FEM_LIP	0,0612	0,0563	0,059	0,0214	0,0277	0,0148
2124	HELD_MAL_LIP	0,1532	0,2284	0,153	0,0434	0,0557	0,0209
2140	HELD_FEM_UEFF	0,0437	0,0427	0,0203	0,009	0,0116	0,0433
2140	HELD_FEM_EFF	0,0174	0,0167	0,0136	0,0082	0,0110	0,0069
2140	HELD_MAL_ADR	0,0596	0,0738	0,0227	0,0301	0,0429	0,008
2140	HELD_FEM_VEFF	0,0915	0,0872	0,0888	0,0284	0,0379	0,0285
2141	HELD_MAL_ADR3ULN	0,0844	0,0968	0,0461	0,0218	0,0238	0,0277
2141	HELD_FEM_UEFF	0,0776	0,0859	0,0221	0,1372	0,1469	
2141	HELD_MAL_ADR	0,0548	0,0515	0,0254	0,0347	0,0399	0.1323
2186	HELD_MAL_ADRSULN	0,0287	0,0843	0,1009	0,0498	0,0718	0,0344
2187	HELD_FEM_ADR3ULN	0,0517	0,0567	0,0507	0,0495	0,0613	0,0798
2192	HELD_FEM_ADR	8000,0	0,0011	0,0003	0,0011	0,0014	0,0529
2192	HELD_FEM_ADR3ULN	0,0114	0,0187	0,0015	0,0146	0,0232	0,0004
2192	HELD_ALL_ADR	0,0234	0,0113	0,0173	0,0053	0,0232	0,0019
2192	HELD_FEM_ADR5ULN	0,0613	0,1149	0,0155	0,073	0,1305	0.0044
2192	HELD_ALL_ADR3ULN	0,1807	0,1865	0,1212	0,0607	0,0756	0,0181
2203	HELD_FEM_LIP	0,0132	0,011	0,0126	0,0101	0,0738	0,039
2203	HELD_ALL_LIP	0,0296	0,0294	0,029	0,042	0,0442	0,0098
2217	HELD_MAL_CC	0,0089	0,0048	0,0053	0,0074	0,0101	0,0422
2217	CVD_FEM	0,1624	0,1741		4,0074	2,0101	0,0071

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	E ROMPARISON AND AND AND AND AND AND AND AND AND AN	<b>cev</b>		E CTVI L EREVA	E   ALLIL E   CPyai		L ALLE
2281	HELD_FEM_CC	0,042	A 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Limited Strains	THE PARTY OF STREET	THE PROPERTY OF THE PARTY OF TH	LERPY
2281	HELD MAL CC	0,052				0,0102	
2284	HELD_MAL_LIP	0,075				0,1238	0,080
2290	HELD_MAL_CC					0,0292	0,013
2327	HELD_MAL_ADR	0,030			0,0022	0,0031	0,0017
2327		0,0279			0,0923	0,1092	. 0,092
. 2327	HELD_MAL_ADR5ULI			0,0381	0,3085	0,4458	0,3068
	HELD_MAL_ADR3UL	0,0396	0,0397	0,0429	0,0919	0,116	0,0897
2327	HELD_FEM_EFF	0,0462	0,0457	0,0458	0,0998	0,1039	0,0998
2353	CVD_MAL	0,0703	0,0407	0,0139	0,0223	0,0233	0,0031
2353	HELD_ALL_CC	0,0255	0,0122	0,0224	0,0659	0,0929	·
2353	CVD_ALL	0,1352	0,1146		0,0468	0,0506	0,0654
2353	HELD_FEM_CC	0,0743	0,0491	0,0628	0,1836	<del></del>	0,0347
2371	HELD_ALL_LIP2	0,018	0,018	0,0181		0,3092	0,1885
2376	HELD_ALL_LIP2	0,03	0,038	<del></del>	0,043	0,0444	0,0432
2401	HELD_FEM_UEFF	0,0263	0,0256	0,0302	0,0327	0,0411	0,0329
2463	HELD_ALL_CC	0,0122		0,0266	0,1128	0,1233	0,1146
2463	HELD_FEM_CC		0,0147	0,0028	0,0144	0,0168	0,0033
2463	HELD_FEM_LIP2	0,0257	0,0328	0,0074	0,0307	0,0376	0,0088
2755		0,0915	0,0988	0,0431	0,7177	0,7419	0,718
	HELD_FEM_ADR	0,0203	0,0192	0,0178	0,0222	0,024	0,022
2755	HELD_ALL_ADR	0,0325	0,035	0,03	0,0499	0,0513	0,0496
2755	HELD_FEM_EFF	0,0455	0,0449	0,0446	0,4065	0,4262	0,4065
2925	HELD_FEM_VEFF	0,0168	0,0169	0,0162	0,0055	0,0058	0,0055
2925	HELD_FEM_UEFF	0,0184	0,0176	0,0181	0,009	0,0119	
3043	HELD_FEM_ADR3ULN	0,031	0,0498	0,0233	0,0515		0,0088
3152	HELD_FEM_VEFF	0,0204	0,0206	0,0196	<del> </del>	0,0764	0,0376
3214	HELD_FEM_VEFF	0,0379	0,0331		0,3254	0,333	0,3253
3215	HELD_MAL_ADR5ULN	0,0093		0,0261	0,4369	0,4475	0,437
3237	HELD_FEM_CC	0,0093	0,1304	0,041	0,0096	0,1304	0,0423
3241	HELD_MAL_ADR		0,0276	0,0167	0,0218	0,0323	0,0211
		0,111	0,1115	0,1048	0,0334	0,0418	0,033
	HELD ALL ADRIULN	0,2155	0,1993	0,0862	0,0716	0,1186	0,0187
	HELD_ALL_ADR5ULN		0,2956	_0,1522	-0,0707-	-0,0873	-0,038
1020	HELD_MAL_ADR3ULN	0,2528	0,2755	0,1635	0,0732	0,1143	0,044

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	P 34 COVE SRISON			Y C Y	ALLEE	MALLEL	ALCEL
3842	CVD_ALL			L DRPVA	E CPYAI	XPVAI	
3842		0,009		0,0014	0,0108	0,0157	0,0016
3842	CVD_MAL	0,0682		0,0207	0,0735	0,1027	0,0222
3843	CVD_FEM	0,0717	7 0,1136	0,0359	0,0751	0,1165	0,0376
3843	HELD_MAL_CC2	0,0207		0,0084	0,0758	0,1046	0,0759
	HELD_FEM_HDL	0,0447	0,024	0,0146	0,1239	0,1687	0,1233
3869	HELD_FEM_UEFF	0,0491	0,0538	0,0488	0,0211	0,0244	0,0202
3942	HELD_FEM_UEFF	0,0206	0,0152	0,0122	0,0028	0,0041	0,0029
4018	HELD_MAL_LIP	0,1128	0,1214	0,0532	0,037	0,0451	0,0313
4206	HELD_ALL_ADR3ULN	0,1055	0,1128	0,1103	0,041	0,0532	0,0418
4206	HELD_FEM_ADR	0,1218	0,1204	0,1193	0,0436	0,0574	0,0416
4206	HELD_ALL_ADR5ULN	0,1204	0,1214	0,1254	0,0472	0,0639	0,0488
4527	· CVD_ALL	0,0044	0,0031	0,0012	0,2436	0,2844	<del> </del>
4527	HELD_FEM_LIP2	0,0441	0,0429	0,0424	0,0147	0,0157	0,2451
4527	HELD_MAL_CC	0,0814	0,0496	0,0661	0,0208	0,0296	0,0145
45.27	HELD_MAL_CC2	0,0599	0,0604	0,0583	0,0256	0,0378	0,0197
4527	HELD_ALL_ADR3ULN	0,0688	0,0608	0,0728	0,0316	0,0402	0,0267
4527	HELD_ALL_CC2	0,1329	0,1396	0,1355	0,0449		0,0354
4527	HELD_ALL_ADR5ULN	0,0796	0,0668	0,1142	0,0478	0,048	0,0461
4544	HELD_MAL_ADR3ULN	0,0116	0,0154	0,0146	0,0043	0,0592	0,0569
4544	HELD_MAL_ADR	0,0731	0,0643	0,0601	0,0283	0,0062	0,0063
4544	HELD_ALL_ADR	0,086	0,0869	0,0832	0,0279	0,0348	0,0274
4544	HELD_ALL_ADR3ULN	0,1284	0,1257	0,1312		0,0308	0,0276
4545	HELD_MAL_ADR3ULN	0,0116	0,0154	0,0146	0,0497	0,054	0,0537
4545	HELD_MAL_ADR	0,0629	0,0569		0,0043	0,0062	0,0063
4545	HELD_ALL_ADR	0,0947	0,0982	0,0516	0,0234	0,0247	0.0226
4668	HELD_ALL_ADRSULN	0,0773	0,0782	0,0917	0,0318	0,0385	0,0314
4669	HELD_FEM_EFF	0,1061	0,1031	0,0348	0,1143	0,1279	0,1111
4718	HELD_MAL_LIP	0,0234		0,1053	0,0415	0,0458	0.0412
4818	HELD_MAL_LIP	0,0234	0,0261	0,006	0;2267	0,2838	0,2221
4827	HELD_MAL_ADR5ULN		0,0073	0,0072	0,0904	0,1138	0,0946
4838	HELD_ALL_CC2		0,0922	0,0873	0,6447	0,708	0,6539
4856	CVD_MAL		0,1425	0,1366	0,047	0,0495	0,0469
L	O.D. MINT	0,0123	0,0338	0,0089	0,0129	0,0349	0,0094

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	COVIPARISON			E GIVE	ALLEL	E2 SALEER	
4868	HELD_MAL_ADR			E TREVA	Mark to the state of the contract of the state of the sta	XPVAI	LRPVA
4868	HELD_MAL_ADRSUL	0,049			0,2125	0,24	0,2117
4887					0,412	0,5267	0,4261
4887	HELD_MAL_CC	0,011		0,0075	0,0066	0,0077	0,0042
4912	HELD_ALL_CC	0,082		0,0811	0,0378	0,0429	0,0378
4951	HELD_MAL_LIP	0,2542	0,3163	0,2499	0,0325	0,053	0,0303
	HELD_ALL_ADR3ULN	1 -	0,0018	0,0018	0,5543	0,6301	0,5547
4951	HELD_FEM_ADR3ULN		0,0029	0,003	0,237	0,284	0,2372
4951	HELD_FEM_ADR5ULN		0,0039	0,0088	0,0663	0,0845	0,0657
4951	HELD_ALL_ADRSULN	0,006	0,0054	0,0103	0,0586	0,0675	
4951	· HELD_FEM_ADR	0,0104	0,0096	0,0091	0,1202	0,1247	0,0589
4951	HELD_ALL_ADR	0,0233	0,0229		0,1271	0,1376	0,12
4952	HELD_ALL_ADR3ULN	0,0018	0,0017	0,0015	0,6771	0,7182	0,1269
4952	HELD_FEM_ADR3ULN	0,0019	0,0017	0,002	0,2491		0,6774
4952	HELD_FEM_ADRSULN	0,0029	0,0023	0,0048	0,0938	0,2848	0,2496
4952	HELD_ALL_ADRSULN	0,0062	0,0056	0,009	0,1013	0,1245	0,094
4966	HELD_MAL_LIP	0,0276	0,027	0,0099	<del></del>	0,1264	0,102
4966	HELD_MAL_ADR	0,0409	0,046	0,0375	0,0138	0,0207	0,0122
4966	HELD_FEM_CC .	0,0951	0,1056	0,0373	0,0937	0,1211	0,0933
5019	CVD_FEM	0,0011	0,001		0,0442	0,0696	. 0,0434
5019	HELD_ALL_CC2	0,0043	<b></b>	0,0007	0,0055	0,0087	0,0053
5019	HELD MAL HDL	0,0666	0,0045	0,0043	0,0479	0,0599	0,0477
5019	HELD_ALL_LIP		0,0705	0,0594	0,0076	0,0117	0,0068
5019	HELD_MAL_CC2	0,0362	0,0383	0,0342	0,0109	0,0125	0,0108
	HELD_FEM_ADR3ULN	0,0182	0,0179	0,0186	0,0143	0,0167	0,0138
	HELD_MAL_ADRSULN	0,0193	0,0172	0,0174	0,064	0,0907	0,0714
5165	•	0,0267	0,0922	0,0873	0,6447	0,708	0,6539
	HELD_FEM_ADR	0,0405	0,0271	0,0268	0,2071	0,2511	0,2059
	HELD_FEM_ADR5ULN	0,0414	0,0557	0,0471	0,0836	0,1012	0,101
5287	HELD_MAL_ADRSULN	0,0556	0,0596	0,1196	0,046	0,0769	0,0577
	HELD_FEM_VEFF	0,0487	0,0497	0,0438	0,0093	0,0101	0,0088
5320	CVD_FEM	0,0342	0,0343	0,0283	0,0279	0,0303	0,0274
5324	HELD_FEM_VEFF	0,0912	0,0915	-0;0898	0,0318	0,0391	
5373 I	TELD_FEM_ADRSULN	0,0095	0,0124	0,0056	0,0061	0,0391	0;0317

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5373		and the same of th	THE SECURE CONTROL	LRPVA	CPYAL	XPVAL	LRPVA
	HELD_ALL_ADR5ULN	., .,	0,0691	0,0342	0,0287	0,0398	0,0217
5375	HELD_FEM_ADR5ULN	-,	0,0136	0,0056	0,0058	0,0081	0,0027
5375	HELD_ALL_ADRSULN	_1 ′	0,1305	0,0564	0,0585	0,0615	0,0495
5376	HELD_MAL_ADR5ULN	0,0067	0,1212	0,0373	0,0069	0,1212	0,0386
5377	HELD_FEM_ADR	0,0201	0,019	0,019	0,2353	0,2692	0,2345
5377	HELD_FEM_ADRSULN	0,0497	0,0546	0,0353	0,0289	0,044	0,0203
5517	HELD_MAL_ADR	0,0831	0,1183	0,0317	0,4341	0,6834	0,4294
5518	HELD_FEM_ADR5ULN	0,0341	0,1839	0,0637	0,0346	0,1839	<del></del>
5564	CVD_MAL	0,0139	0,0146	0,0159	0,1077	0,1348	0,0647
5569	HELD_MAL_ADR5ULN	0,1012	0,1304	0,0676	0,0445	0,0667	0,1057
5569	HELD_ALL_ADR5ULN	0,1458	0,1504	0,0609	0,0502	0,0672	0,0238
5716	HELD_ALL_ADR3ULN	0,0067	0,0064	0,0069	0,0024		0,04
5716	HELD_FEM_ADR3ULN		0,0063	0,0059	0,0027	0,0025	0,0023
5716	HELD_ALL_ADR5ULN	· ·	0,0232	0,0218	0,0027	. 0,0037	0,0024
5716	HELD_FEM_ADRSULN	0,0769	0,0784	0,0685		`0,0124	0,0092
5717	HELD_ALL_ADRSULN	0,1212	0,1272	0,0083	0,0334	0,0412	0,0321
5717	CVD_FEM	0,0496	0,0575	0,0431	0,0433	0,049	0,0427
5850	HELD_MAL_CC	0,0304	0,0344		0,0551	0,0634	0,054
5959	CVD_MAL	0,064	0,0647	0,0113	0,1197	0,1794	0,1186
6151	HELD_MAL_ADR	0,0502		0,0552	0,0467	0,0678	0,048
6236	HELD ALL ADR		0,0501	0,0488	0,3223	0,3964	0,3221
6277	HELD_FEM_ADRSULN	0,0472	0,051	0,0424	0,0867	0,0953	0,0864
6277	HELD_ALL_ADRSULN	0,0014	0,0053	0,0049	0,0127	0,0215	0,0185
6277		0,0041	0,0135	0,026	0,0832	0,1012	0,0964
6277	HELD_FEM_ADR	0,0251	0,0239	0,0079	0,0157	0,0186	0,0149
6313	HELD_FEM_ADR3ULN	0,0147	0,0126	0,0119	0,0167	0,02	0,0196
6369	HELD_FEM_UEFF	0,0369	0,0357	0,0376	0,1201	0,1519	0,1204
	HELD_FEM_LIP	0,1311	0,145	0,1269	0,0461	0,0594	0,0457
6374	HELD_ALL_ADR3ULN	0,0338	0,0325	0,0352	0,0091	0,0107	0,0099
6374	HELD_MAL_ADR3ULN	0,0498	0,0564	0,044	0,011	0,0152	0,0121
6396	HELD_MAL_CC	0,0165	0,0238	0,0048	0,0233	0,031	0,0066
6396	HELD_ALL_CC	0,0528	0,0316	0,0496	0,0334	0,0403	0,0323
6396	CVD_FEM.	0,1144	0,0874	0,0928	0,046	0,0631	0,0323

	P COMPARISON	Paralle Assertion	E Xiv	L LRPV	E ALLEY L CPVAL	id the latest property	
6396	CVD_ALL	0,138	8 0,121	3 0,093			LRPVA
6486	HELD_ALL_CC2	0,144					0,0465
6520	HELD_MAL_ADR5UL	N 0,000				0,0528	0,0345
6520	HELD_MAL_ADR3UL					0,3068	0,2137
6520	HELD_ALL_ADR5ULN	-				0,2122	0,1939
6520	HELD_MAL_ADR	0,074				0,0892	0,093
6522	HELD_FEM_ADR3ULN		`			0,3417	0,3212
6522	HELD_FEM_ADR	0,0523				0,3091	0,284
6524	HELD_MAL_ADR3ULN				0,0894	0,0983	0,0882
6596	HELD_FEM_ADR3ULN			0,0096	0,0128	0,0173	0,0106
6596	HELD_FEM_ADR5ULN	<u> </u>	0	O.	0	0,0001	0
6596					0,0001	1100,0	0,0008
6596	HELD_ALL_ADR3ULN			0,0005	0,0005	0,001	0,001
6596	HELD_FEM_ADR	0,0008		0,0005	0,0014	0,0018	0,0009
	HELD_ALL_ADRSULN			0,0064	0,0036	0,0085	0,0094
6596	HELD_ALL_ADR	0,0199	0,0229	0,0186	0,0253	0,0286	0,0236
6734	HELD_ALL_CC	0,04	0,0752	0,0208	0,0463	0,0816	0,0241
6743	HELD_ALL_ADR	0,0299	0,0298	0,0293	0,5743	0,6388	0,5742
7128	HELD_ALL_ADR3ULN	0,0099	0,0103	0,0081	0,0032	0,0042	0,0021
7128	HELD_FEM_ADR3ULN	0,0161	0,014.	0,0134	0,011	0,0121	
7128	HELD_ALL_ADR5ULN	0,0787	0,0793	0,0702	0,029	0,0316	0,0085
7128	HELD_FEM_ADR	0,0447	0,0497	0,0437	0,0497	0,0519	0,0217
7128	HELD_FEM_ADRSULN	0,0996	0,1085	0,0925	0,0561		0,0496
7363	HELD_FEM_LIP	0,0763	0,0816	0,0701		0,0763	0,0458
7363	HELD_ALL_LIP	0,0741	0,0762	0,0712	0,0282	0,0385	0,0276
7409	HELD_FEM_ADR5ULN	0,0051	0,0049	0,01	0,0298	0,0314	0,0299
	HELD_FEM_ADR3ULN	0,0303	0,0175		0,0025	0,0051	0,0054
	HELD_MAL_ADR5ULN	0,1823	0,1987	0,0316	0,0135	0,0165	0,0172
8138	HELD_MAL_LIP	0,0177		0,0669	0,0691	0,128	0,017
8138	HELD_MAL_CC	0,0177	0,0193	0,0183	0,0079	0,0088	0,0069
3138	TYPY TO LET		0,011	0,0077	0,4323	0,4651	0,4318
3168	TIET TO A COMMISSION	0,0401	0,039	0,0399	0,0761	0,0923	0,0757
168	THE P. ST.	0,0229	0,0222	0,026	0,011	0,0203	0,0132
		0,0241	0,0204	0,0226	0,1027	0,1374	0,1017

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8210	HELD_ALL_ADR3UL	20,009		- red by a last state of the	AND DESCRIPTIONS OF THE PARTY.	क्रायक स्वास्त्रकरूप	LRPVA
8210	HELD_FEM_ADR3UL					0,8049	0,7818
8210	HELD_FEM_ADR	0,022	,			0,4314	0,4063
8210	HELD ALL ADR	0,021			0,2153	0,2257	0,2151
8241	HELD_FEM_LIP	0,0213		0,0203	0,2277	0,2424	0,2276
8241	HELD_ALL_LIP				0,0063	0,0082	0,0058
8249	HELD_ALL_ADR3ULN	0,159			0,0425	0,0474	0,0407
8249	HELD_ALL_ADR5ULN			-	0,0458	0,0517	0,0569
8480				0,0653	0,0527	0,0943	0,0765
8480	CVD_FEM	0,0462		0,0232	0,0026	0,0039	0,0008
8577	CVD_MAL	0,1317	0,1542	0,0466	0,0145	0,0286	0,0026
· · · · · · · · · · · · · · · · · · ·	HELD_ALL_ADR3ULN	1	0,0657	0,0615	0,0252	0,0333	0,0264
8577	HELD_ALL_ADR	0,0786	0,0752	0,0779	0,0341	0,0374	0,0339
8577	HELD_ALL_ADRSULN		0,1417	0,1606	0,05	0,0577	0,0532
8578	HELD_ALL_ADR3ULN	0,0857	0,0895	0,0777	0,0407	0,0491	0,0421
8653	HELD_MAL_ADR	0,0015	0,002	0,0012	0,004	0,005	0,0032
8653	HELD_MAL_ADR3ULN	0,0104	0,0118	0,0049	0,0239	0,0259	0,0099
8653	HELD_MAL_ADR5ULN	0,0243	0,0358	0,0061	0,0499	0,0688	0,0107
8653	HELD_ALL_ADRJULN	0,0509	0,0714	0,04	. 0,0799	0,1109	
8816	HELD_FEM_LIP2	0,0115	0,0116	0,0106	0,0057	0,0067	0,0679
8816	HELD_FEM_HDL	0,0254	0,0258	0,0184	0,0126	0,0148	0,0056
8816	HELD_ALL_CC2	0,0198	0,0205	0,0188	0,0120		0,0119
8816	CVD_ALL	0,0862	0,084	0,0801		0,0373	0,0354
8816	HELD_FEM_CC2	0,0732	0,0788	0,0699	0,0253	0,0334	. 0,0231
8816	HELD_MAL_HDL	0,0827	0,0805		0,0263	0,0349	0,0263
8931	HELD_FEM_ADR3ULN	0,0638		0,0459	0,9552	1	0,9552
8943	HELD_MAL_ADR3ULN	0,115	0,0558	0,0365	0,1009	0,1129	0,0851
9243	HELD_FEM_VEFF		0,1264	0,0702	0,0366	0,0409	0,0217
9243	HELD_MAL_ADRSULN	0,0407	0,0439	0,0252	0,155	0,1691	0,1544
9243 •	HELD_FEM_UEFF	0,1035	0,0777	0,0285	0,2159	0,2497	0,1855
9523	HELD_MAL_ADRSULN	0,1004	0,12	0,0335	0,1733	0,2118	0,1696
9940	77777	0,0425	0,0646	0,0613	0,0575	0,0785	0,0889
9940			0,0425	0,0073	0,0294	0,0542	0,0099
,,,,,	HELD_ALL_CC	0,0341	0,0266	0,0312	0,0231	0,0354	0,0225

		BAYS	P COMPARSON	i (GIV	PE GIV	e keng	is artic	e allei	EJALLE	eri ir.
10591   Held_RLL_ADSJUIN   0,0852   0,0819   0,1028   0,0428   0,0524   0,0487   0,0487   10541   Held_FEM_UEFF   0,0349   0,0191   0,0267   0,0305   0,0477   0,0256   10541   Held_FEM_VEFF   0,066   0,0484   0,0643   0,0206   0,0217   0,022   10600   CVD_MAL   0,0475   0,0359   0,0348   0,0046   0,0121   0,0029   10600   Held_ALL_HDL   0,0267   0,0298   0,0058   0,0231   0,0325   0,0064   10600   Held_MAL_HDL   0,056   0,1137   0,0231   0,0625   0,1228   0,0256   10745   Held_MAL_LIP   0,056   0,1137   0,025   0,0255   0,1228   0,0256   10748   Held_MAL_LIP   0,1405   0,1855   0,1371   0,05   0,0676   0,0547   10749   Held_FEM_LIP   0,0593   0,0591   0,055   0,0232   0,026   0,023   10745   CVD_MAL   0,1111   0,1415   0,1247   0,0383   0,0491   0,0448   10811   Held_FEM_LIP   0,0827   0,0859   0,0821   0,0442   0,0465   0,0435   10811   CVD_ALL   0,1149   0,1091   0,1111   0,0524   0,0646   0,0498   10830   Held_ALL_LIP   0,0065   0,0065   0,0065   0,0036   0,0039   0,0036   10830   Held_ALL_LIP   0,0187   0,0197   0,0187   0,011   0,0112   0,0112   0,0103   10830   Held_MAL_LIP   0,0742   0,0873   0,0238   0,011   0,0112   0,0103   10830   Held_MAL_LIP   0,0742   0,0873   0,0613   0,0224   0,0279   0,0219   10830   Held_MAL_LIP   0,0742   0,0873   0,0613   0,0224   0,0279   0,0219   10830   Held_MAL_LIP   0,0742   0,0873   0,0613   0,0224   0,0279   0,0219   10949   Held_FEM_VEFF   0,0543   0,0777   0,0536   0,0355   0,044   0,0356   10949   Held_FEM_VEFF   0,0543   0,0777   0,0536   0,0352   0,0374   0,0356   10966   Held_ALL_ADR3UIN   0,1473   0,1615   0,043   0,0258   0,0457   0,0177   10962   Held_ALL_ADR3UIN   0,1473   0,1615   0,043   0,0556   0,044   0,0356   10966   Held_ALL_ADR3UIN   0,1473   0,1615   0,043   0,0557   0,0794   0,0487   10966   Held_ALL_ADR3UIN   0,1473   0,1615   0,043   0,0556   0,044   0,0356   0,0356   0,0356   0,0348   0,0356   0,0356   0,0348   0,0348   0,00375   0,0151   0,0112   0,0102   0,0666   0,0666   0,0666   0,0658   0,0667   0,0618   0,0667   0,0618   0,0667   0,0618		**********		GPV	IE VPV	L PRPV	L CPVA		3.61 14 12 17 7	27 L
10541   HELD_FEM_UEFF   0.0349   0.0191   0.0267   0.0305   0.0477   0.0256     10600   CVD_MAL   0.0475   0.0359   0.0348   0.0046   0.0121   0.0029     10600   HELD_ALL_HDL   0.0207   0.0258   0.0058   0.0231   0.0325   0.0064     10600   HELD_MAL_HDL   0.0566   0.1137   0.0231   0.0625   0.1228   0.0256     10745   HELD_MAL_LIP   0.0926   0.0862   0.085   0.056   0.0701   0.0491     10748   HELD_MAL_LIP   0.0926   0.0862   0.085   0.056   0.0701   0.0491     10749   HELD_FEM_LIP   0.0593   0.0591   0.055   0.0032   0.0266   0.0547     10811   HELD_FEM_LIP   0.0827   0.0859   0.0821   0.0442   0.0465   0.0435     10811   CVD_ALL   0.1149   0.1091   0.1111   0.0524   0.0665   0.0435     10830   HELD_ALL_LIP   0.0065   0.0065   0.0062   0.0036   0.0039   0.0036     10830   HELD_ALL_LIP   0.0187   0.0191   0.018   0.0037   0.0048   0.0037     10830   HELD_MAL_LIP   0.0389   0.0395   0.0038   0.0011   0.0112   0.0109     10830   HELD_ALL_LIP   0.0187   0.0191   0.018   0.0037   0.0048   0.0037     10830   HELD_MAL_LIP   0.0389   0.0395   0.0383   0.011   0.0112   0.0109     10830   HELD_FEM_LIP   0.0742   0.0873   0.0613   0.0224   0.0279   0.0219     10830   HELD_FEM_LIP   0.0748   0.0744   0.0743   0.0356   0.0440   0.0356     10949   HELD_FEM_LIP   0.0544   0.0743   0.0356   0.044   0.0356     10949   HELD_FEM_LIP   0.0544   0.0744   0.0743   0.0356   0.044   0.0356     10949   HELD_FEM_LIP   0.0748   0.0744   0.0743   0.0356   0.044   0.0356     10960   HELD_ALL_ADR3ULN   0.1473   0.1615   0.043   0.0256   0.044   0.0356     10960   HELD_ALL_ADR3ULN   0.1473   0.1615   0.043   0.0556   0.044   0.0488     10960   HELD_ALL_ADR3ULN   0.1473   0.1615   0.043   0.0556   0.044   0.0488     11000   HELD_MAL_LIP2   0.0379   0.0378   0.0554   0.0357   0.0125   0.0143     11000   HELD_MA		<b></b>		N 0,085	0,081			A LE P. M. Sept. O. S.	The wastern	<u> </u>
10341   HELD_FEM_VEFF   0,066   0,0484   0,0643   0,0206   0,0217   0,022		<u> </u>	- LINE OEFF	0,034	9 0,019	0,026				
10600   CVD_MAL   0,0475   0,0359   0,0348   0,0046   0,0121   0,0029				0,06	6 0,048	4 0,0643				
10600   HELD_ALL_HDL   0,0207   0,0298   0,0058   0,0231   0,0325   0,0064				0,047	5 0,035					
10600   HELD_MAL_HDL   0,056   0,1137   0,0231   0,0625   0,1228   0,0256		10600	HELD_ALL_HDL	0,020	7 0,029					
10745   HELD_MAL_LIP   0,0926   0,0862   0,085   0,056   0,0701   0,0491		10600	HELD_MAL_HDL	0,056	5 0,113		-,			
10748		10745	HELD_MAL_LIP	0,092						
10749		10748	HELD_MAL_LIP	0,140						1
10785		10749	HELD_FEM_LIP							
10811		10785	· CVD_MAL						0,023	
10811		10811	HELD_FEM_LIP2						0,0448	3
10830   HELD_ALL_LIP2   0,0065   0,0065   0,0062   0,0036   0,0039   0,0036   10830   HELD_MAL_LIP2   0,0187   0,0191   0,018   0,0037   0,0048   0,0037   10830   HELD_MAL_LIP2   0,0389   0,0395   0,0383   0,011   0,0112   0,0109   10830   CVD_FEM   0,0268   0,0239   0,0238   0,0125   0,0141   0,0121   10830   HELD_MAL_LIP   0,0742   0,0873   0,0613   0,0224   0,0279   0,0219   10830   HELD_FEM_LIP   0,1364   0,1403   0,134   0,0428   0,0556   0,0426   10949   HELD_FEM_VEFF   0,0543   0,0577   0,0536   0,0352   0,0374   0,0351   10949   HELD_FEM_EFF   0,0748   0,0744   0,0743   0,0356   0,04   0,0356   10962   CVD_FEM   0,0113   0,0275   0,0091   0,0218   0,0457   0,0177   10962   HELD_ALL_ADR3ULN   0,1473   0,1615   0,043   0,2642   0,3199   0,258   10966   HELD_ALL_ADR3ULN   0,1289   0,1277   0,0351   0,1511   0,1736   0,1447   10966   HELD_ALL_ADRSULN   0,1509   0,1612   0,0683   0,0587   0,0794   0,0483   11000   HELD_MAL_LIP2   0,0379   0,0378   0,0375   0,0125   0,0143   0,0123   11000   HELD_MAL_ADRSULN   0,0414   0,0384   0,0554   0,0307   0,0378   0,0344   11000   HELD_MAL_ADRSULN   0,0414   0,0384   0,0554   0,0307   0,0378   0,0348   11000   HELD_MAL_ADRSULN   0,0414   0,0384   0,0554   0,0307   0,0378   0,0348   11000   HELD_MAL_ADRSULN   0,0477   0,0555   0,0961   0,0351   0,0358   0,0348   11000   HELD_MAL_ADRSULN   0,0477   0,0555   0,0971   0,053   0,0607   0,0618   11001   HELD_MAL_LIP2   0,03   0,0682   0,0688   0,0235   0,0241   0,00232   11001   HELD_MAL_LIP2   0,0362   0,0652   0,0658   0,0955   0,00241   0,00232   11001   HELD_MAL_LIP2   0,0362   0,0652   0,0658   0,00235   0,00241   0,00232   11001   HELD_MAL_LIP2   0,0662   0,0652   0,0658   0,00235   0,00241   0,00232   11001   HELD_MAL_LIP2   0,0662   0,0652   0,0658   0,00255   0,00241   0,00232   11001   HELD_MAL_LIP2   0,0662   0,0652   0,0658   0,00255   0,00241   0,00232   11001   HELD_MAL_LIP2   0,0662   0,0652   0,0658   0,00255   0,00241   0,00232   11001   0,00241   0,00232   0,00266   0,00525   0,00241   0,00232   11001   0		10811							0,0435	$\Box$
10830		10830							0,0498	
10830   HELD_MAL_LIP2   0,0389   0,0395   0,0383   0,011   0,0112   0,0109		10830	<del></del>					0,0039	0,0036	$\Box$
10830		10830						0,0048	0,0037	$\exists$
10830   HELD_MAL_LIP   0,0742   0,0873   0,0613   0,0224   0,0279   0,0219	ı	10830	<u> </u>				0,011	0,0112	0,0109	$\exists$
10830         HELD_FEM_LIP         0,0742         0,0873         0,0613         0,0224         0,0279         0,0219           10949         HELD_FEM_VEFF         0,0543         0,0577         0,0536         0,0352         0,0374         0,0351           10949         HELD_FEM_EFF         0,0748         0,0744         0,0743         0,0356         0,04         0,0356           10962         CVD_FEM         0,0113         0,0275         0,0091         0,0218         0,0457         0,0177           10962         HELD_ALL_ADR3ULN         0,1473         0,1615         0,043         0,2642         0,3199         0,258           10966         HELD_ALL_ADR3ULN         0,1289         0,1277         0,0351         0,1511         0,1736         0,1447           10966         HELD_ALL_ADRSULN         0,1509         0,1612         0,0683         0,0587         0,0794         0,0483           11000         HELD_MAL_LIP2         0,0379         0,0378         0,0375         0,0125         0,0143         0,0123           11000         HELD_MAL_ADR3ULN         0,0414         0,0384         0,0554         0,0307         0,0378         0,0344           11000         HELD_MAL_LIP2         0,0965	ŀ			<del>- </del>	-	-	0,0125	0,0141	0,0121	$\dashv$
10949         HELD_FEM_VEFF         0,0543         0,1303         0,134         0,0428         0,0556         0,0426           10949         HELD_FEM_EFF         0,0748         0,0744         0,0743         0,0356         0,04         0,0356           10962         CVD_FEM         0,0113         0,0275         0,0091         0,0218         0,0457         0,0177           10962         HELD_ALL_ADR3ULN         0,1473         0,1615         0,043         0,2642         0,3199         0,258           10966         HELD_ALL_ADR3ULN         0,1289         0,1277         0,0351         0,1511         0,1736         0,1447           10966         HELD_ALL_ADRSULN         0,1509         0,1612         0,0683         0,0587         0,0794         0,0483           11000         HELD_MAL_LIP2         0,0379         0,0378         0,0375         0,0125         0,0143         0,0123           11000         CVD_FEM         0,0202         0,0198         0,0161         0,9584         1         0,9584           11000         HELD_MAL_ADR3ULN         0,0414         0,0384         0,0554         0,0307         0,0378         0,0348           11000         HELD_MAL_ADRSULN         0,0477	ŀ					0,0613	0,0224	0,0279	0,0219	7
10949         HELD_FEM_EFF         0,0748         0,0744         0,0743         0,0352         0,0374         0,0351           10962         CVD_FEM         0,0113         0,0275         0,0091         0,0218         0,0457         0,0177           10962         HELD_ALL_ADR3ULN         0,1473         0,1615         0,043         0,2642         0,3199         0,258           10966         HELD_ALL_ADR3ULN         0,1289         0,1277         0,0351         0,1511         0,1736         0,1447           10966         HELD_ALL_ADR5ULN         0,1509         0,1612         0,0683         0,0587         0,0794         0,0483           11000         HELD_MAL_LIP2         0,0379         0,0378         0,0375         0,0125         0,0143         0,0123           11000         CVD_FEM         0,0202         0,0198         0,0161         0,9584         1         0,9584           11000         HELD_MAL_ADR3ULN         0,0414         0,0384         0,0554         0,0307         0,0378         0,0344           11000         HELD_MAL_ADRSULN         0,0477         0,0555         0,096         0,0351         0,0358         0,0348           11001         HELD_MAL_LIP2         0,03	ŀ		<del></del>	<del></del>		0,134	0,0428	0,0556	0,0426	$\dashv$
10962   CVD_FEM   0,0748   0,0744   0,0743   0,0356   0,04   0,0356   10962   CVD_FEM   0,0113   0,0275   0,0091   0,0218   0,0457   0,0177   10962   HELD_ALL_ADR3ULN   0,1473   0,1615   0,043   0,2642   0,3199   0,258   10966   HELD_ALL_ADR3ULN   0,1289   0,1277   0,0351   0,1511   0,1736   0,1447   10966   HELD_ALL_ADR5ULN   0,1509   0,1612   0,0683   0,0587   0,0794   0,0483   11000   HELD_MAL_LIP2   0,0379   0,0378   0,0375   0,0125   0,0143   0,0123   11000   CVD_FEM   0,0202   0,0198   0,0161   0,9584   1   0,9584   1   11000   HELD_MAL_ADR3ULN   0,0414   0,0384   0,0554   0,0307   0,0378   0,0348   11000   HELD_MAL_ADR3ULN   0,0414   0,0384   0,0554   0,0307   0,0358   0,0348   11000   HELD_MAL_ADRSULN   0,0477   0,0555   0,096   0,0351   0,0358   0,0348   11001   HELD_MAL_LIP2   0,03   0,0288   0,0297   0,0103   0,0111   0,0102   11001   HELD_ALL_LIP2   0,0662   0,0652   0,0658   0,0235   0,0241   0,0232   11001   CVD_FEM   0,0325   0,0293   0,0266   0,0256   0,0241   0,0232   11001   0,000000000000000000000000000	ŀ			+	0,0577	0,0536	0,0352	0,0374	0,0351	$\exists$
10962         HELD_ALL_ADR3ULN         0,0113         0,0275         0,0091         0,0218         0,0457         0,0177           10962         HELD_ALL_ADR3ULN         0,1473         0,1615         0,043         0,2642         0,3199         0,258           10966         HELD_ALL_ADR3ULN         0,1289         0,1277         0,0351         0,1511         0,1736         0,1447           10966         HELD_ALL_ADR5ULN         0,1509         0,1612         0,0683         0,0587         0,0794         0,0483           11000         HELD_MAL_LIP2         0,0379         0,0378         0,0375         0,0125         0,0143         0,0123           11000         CVD_FEM         0,0202         0,0198         0,0161         0,9584         1         0,9584           11000         HELD_MAL_ADR3ULN         0,0414         0,0384         0,0554         0,0307         0,0378         0,0344           11000         HELD_ALL_LIP2         0,0965         0,0965         0,096         0,0351         0,0358         0,0348           11001         HELD_MAL_ADRSULN         0,0477         0,0555         0,0971         0,053         0,0607         0,0618           11001         HELD_MAL_LIP2         0,0662	-				0,0744	0,0743	0,0356	0,04		$\dashv$
10966         HELD_ALL_ADR3ULN         0,1473         0,1615         0,043         0,2642         0,3199         0,258           10966         HELD_ALL_ADR3ULN         0,1289         0,1277         0,0351         0,1511         0,1736         0,1447           10966         HELD_ALL_ADR5ULN         0,1509         0,1612         0,0683         0,0587         0,0794         0,0483           11000         HELD_MAL_LIP2         0,0379         0,0378         0,0375         0,0125         0,0143         0,0123           11000         CVD_FEM         0,0202         0,0198         0,0161         0,9584         1         0,9584           11000         HELD_MAL_ADR3ULN         0,0414         0,0384         0,0554         0,0307         0,0378         0,0344           11000         HELD_ALL_LIP2         0,0965         0,0965         0,096         0,0351         0,0358         0,0348           11001         HELD_MAL_LIP2         0,03         0,0288         0,0297         0,0103         0,0111         0,0102           11001         HELD_ALL_LIP2         0,0662         0,0652         0,0658         0,0235         0,0241         0,0232           11001         CVD_FEM         0,0325         0,	ŀ			0,0113	0,0275	0,0091	0,0218	0,0457	<del></del>	$\dashv$
10966         HELD_ALL_ADR3ULN         0,1289         0,1277         0,0351         0,1511         0,1736         0,1447           10966         HELD_ALL_ADR5ULN         0,1509         0,1612         0,0683         0,0587         0,0794         0,0483           11000         HELD_MAL_LIP2         0,0379         0,0378         0,0375         0,0125         0,0143         0,0123           11000         CVD_FEM         0,0202         0,0198         0,0161         0,9584         1         0,9584           11000         HELD_MAL_ADR3ULN         0,0414         0,0384         0,0554         0,0307         0,0378         0,0344           11000         HELD_ALL_LIP2         0,0965         0,0965         0,096         0,0351         0,0358         0,0348           11000         HELD_MAL_ADRSULN         0,0477         0,0555         0,0971         0,053         0,0607         0,0618           11001         HELD_MAL_LIP2         0,03         0,0288         0,0297         0,0103         0,0111         0,0102           11001         HELD_ALL_LIP2         0,0662         0,0652         0,0658         0,0235         0,0241         0,0232           11001         CVD_FEM         0,0325         0	F			0,1473	0,1615	0,043	0,2642	0,3199		$\dashv$
10900         HELD_ALL_ADRSULN         0,1509         0,1612         0,0683         0,0587         0,0794         0,0483           11000         HELD_MAL_LIP2         0,0379         0,0378         0,0375         0,0125         0,0143         0,0123           11000         CVD_FEM         0,0202         0,0198         0,0161         0,9584         1         0,9584           11000         HELD_MAL_ADRSULN         0,0414         0,0384         0,0554         0,0307         0,0378         0,0344           11000         HELD_ALL_LIP2         0,0965         0,0965         0,096         0,0351         0,0358         0,0348           11001         HELD_MAL_ADRSULN         0,0477         0,0555         0,0971         0,053         0,0607         0,0618           11001         HELD_MAL_LIP2         0,03         0,0288         0,0297         0,0103         0,0111         0,0102           11001         HELD_ALL_LIP2         0,0662         0,0652         0,0658         0,0235         0,0241         0,0232           11001         CVD_FEM         0,0325         0,0293         0,0266         0,0658         0,0235         0,0241         0,0232	L			0,1289	0,1277	0,0351	0,1511	ļ	<u> </u>	-
11000         HELD_MAL_LIP2         0,0379         0,0378         0,0375         0,0125         0,0143         0,0123           11000         CVD_FEM         0,0202         0,0198         0,0161         0,9584         1         0,9584           11000         HELD_MAL_ADR3ULN         0,0414         0,0384         0,0554         0,0307         0,0378         0,0344           11000         HELD_ALL_LIP2         0,0965         0,0965         0,096         0,0351         0,0358         0,0348           11001         HELD_MAL_ADRSULN         0,0477         0,0555         0,0971         0,053         0,0607         0,0618           11001         HELD_MAL_LIP2         0,03         0,0288         0,0297         0,0103         0,0111         0,0102           11001         HELD_ALL_LIP2         0,0662         0,0652         0,0658         0,0235         0,0241         0,0232           11001         CVD_FEM         0,0325         0,0293         0,0266         0,0658         0,0235         0,0241         0,0232	L			0,1509	0,1612	0,0683	0,0587		<del> </del>	4
11000         CVD_FEM         0,0202         0,0198         0,0161         0,9584         1         0,9584           11000         HELD_MAL_ADR3ULN         0,0414         0,0384         0,0554         0,0307         0,0378         0,0344           11000         HELD_ALL_LIP2         0,0965         0,0965         0,096         0,0351         0,0358         0,0348           11000         HELD_MAL_ADR5ULN         0,0477         0,0555         0,0971         0,053         0,0607         0,0618           11001         HELD_MAL_LIP2         0,03         0,0288         0,0297         0,0103         0,0111         0,0102           11001         HELD_ALL_LIP2         0,0662         0,0652         0,0658         0,0235         0,0241         0,0232           11001         CVD_FEM         0,0325         0,0293         0,0266         0,0746         0,0746         0,0241         0,0232	L			0,0379	0,0378	0,0375		<del></del>		4
11000         HELD_MAL_ADR3ULN         0,0414         0,0384         0,0554         0,0307         0,0378         0,0344           11000         HELD_ALL_LIP2         0,0965         0,0965         0,096         0,0351         0,0358         0,0348           11000         HELD_MAL_ADR5ULN         0,0477         0,0555         0,0971         0,053         0,0607         0,0618           11001         HELD_MAL_LIP2         0,03         0,0288         0,0297         0,0103         0,0111         0,0102           11001         HELD_ALL_LIP2         0,0662         0,0652         0,0658         0,0235         0,0241         0,0232           11001         CVD_FEM         0,0325         0,0293         0,0266         0,0740         0,0241         0,0232	L			0,0202	0,0198	0,0161	<u> </u>			4
11000         HELD_ALL_LIP2         0,0965         0,0965         0,0965         0,096         0,0351         0,0358         0,0348           11000         HELD_MAL_ADRSULN         0,0477         0,0555         0,0971         0,053         0,0607         0,0618           11001         HELD_MAL_LIP2         0,03         0,0288         0,0297         0,0103         0,0111         0,0102           11001         HELD_ALL_LIP2         0,0662         0,0652         0,0658         0,0235         0,0241         0,0232           11001         CVD_FEM         0,0325         0,0293         0,0266         0,0740         0,0241         0,0232	L		HELD_MAL_ADR3ULN	0,0414	0,0384	0,0554	<del></del>			1
11000       HELD_MAL_ADR5ULN       0,0477       0,0555       0,0971       0,053       0,0607       0,0618         11001       HELD_MAL_LIP2       0,03       0,0288       0,0297       0,0103       0,0111       0,0102         11001       HELD_ALL_LIP2       0,0662       0,0652       0,0658       0,0235       0,0241       0,0232         11001       CVD_FEM       0,0325       0,0293       0,0266       0,0743			HELD_ALL_LIP2	0,0965	0,0965					1
11001         HELD_MAL_LIP2         0,03         0,0288         0,0297         0,0103         0,0111         0,0102           11001         HELD_ALL_LIP2         0,0662         0,0652         0,0658         0,0235         0,0241         0,0232           11001         CVD_FEM         0,0325         0,0293         0,0266         0,0743		11000	HELD_MAL_ADR5ULN	0,0477						]
11001 HELD_ALL_LIP2		11001	HELD_MAL_LIP2							]
1 1001 CVD_FEM 0,0325 0,0293 0,0265 0,0241 0,0232	_	11001							0,0102	1
- 1 VVVIV   V.V.Y3   1 111766   0 0040	_	11001						0,0241	0,0232	-
					0,0293	U,U266	0,9749	1	0,9749	l

BAXSNE		GIVE		G W	CALLERY COLUMNIA		511 P. A. (518 T. 1877 P. 1877 P. 18
11001	The state of the s		- ciberelier vibrefix	Riev	L CPYAL	XPVAL	LRPVAL
11001	HELD_MAL_ADR3ULI			0,0554	0,0307	0,0378	0,0344
11020	HELD_ALL_LIP	0,1116		0,1013	0,0482	0,057	0,0473
	HELD_MAL_ADR3UL	0,1685	0,1457	0,087	0,0596	0,0761	0,049
11073	HELD_FEM_LIP	0,111	0,1116	0,1085	0,0331	0,0361	0,0328
11073	HELD_ALL_CC2	0,096	0,0963	0,0954	0,0453	0,0475	0,0328
11192	HELD_FEM_ADR5ULN	0,0153	0,0191	0,0329	0,2812		
11192.	HELD_FEM_ADR3ULN	0,0257	0,0216	0,0353	0,2446		0,2893
11248	HELD_FEM_ADR3ULN	0,0183		0,0137	0,025	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	0,249
11248	HELD_ALL_ADR	0,1078	0,1144	0,1071		0,0322	0,0203
11410	HELD_FEM_VEFF	0,0091	0,0089		0,042	0,0434	0,0419
11448	HELD MAL HDL	0,0019		0,0085	0,088	0,0909	0,0879
11448	HELD_MAL_LIP		0,0012	0,0015	0,0002	0,0003	0,0002
11448	HELD_MAL_LIP2	0,0055	0,0027	0,0061	0,0034	0,005	0,0042
11448		0,0059	0,0056	0,0058	0,0233	0,0245	0,0234
	HELD_ALL_LIP2	0,0108	0,0106	0,0109	0,0119	0,0124	0,012
11448	HELD_ALL_HDL	0,0647	0,0708	0,0648	0,0138	0,0215	0,0142
11448	HELD_FEM_ADR	0,0637	0,0601	0,0603	0,0162	0,0199	0,0156
11448	HELD_ALL_ADR	0,0576	0,0568	0,055	0,017	0,0209	0,0166
11448	HELD_ALL_CC	0,0976	0,1314	0,0453	0,0671	0,0727	
11450	HELD_MAL_LIP	0,0068	0,0052	0,0066	0,0007	<del> </del>	0,0652
11456	CVD_FEM	0,0026	0,0043	0,0016		0,0012	0,0009
11462	HELD_MAL_LIP2	0,0302	0,0225	0,0284	0,0038	0,0058	0,0023
11462	HELD ALL LIP2	0,0406	0,0368		0,0091	0,0109	0,0091
11483	HELD_FEM_ADR5ULN	0,032		0,0362	0,0384	0,0431	0,0387
	HELD_FEM_ADR3ULN		0,0455	0,0589	0,0562	0,0771	0,0832
11483	HELD_FEM_ADR	0,0442	0,034	0,0495	0,0824	0,0989	0,0958
11531		0,0628	0,0468	0,045	0,1531	0,2	0,1477
11536	HELD_FEM_CC	0,1229	0,1273	0,0498	0,0189	0,0335	0,0137
	HELD_ALL_CC	0,0789	0,085	0,0365	0,7564	0,8525	0,7562
14537	HELD_MAL_ADR	0,1696	0,1625	0,1616	0,0467	0,0604	0,0455
11558	HELD_MAL_LIP2	0,0028	0,0023	0,0028	0,0058	0,0064	
11558	HELD_ALL_LIP2	0,011	0,0105	0,011	0,005		0,0058
11558	HELD_ALL_CC		0,0503	0,05		0,0054	0,005
11585	HELD_MAL_CC		0,0372	0,0136	0,102	0,1242	0,1013
			4,0372	0,0130	0,0108	0,0193	0,0094

BAYSN			L GUYE		E ALLEL	EIZEDEL	.15531161.65912312.655.25
11594				L I RPV	E CRYA	XPVAI	LRPVA
11594		0,001	9 0,099	8 0,035	0,0195	0,0196	0,0069
	HELD_MAL_ADR	0,031			0,0365	0,0462	0,0324
11614	HELD_FEM_CC	0,047	3 0,057	7 0,0234	0,0572	0,0644	0,0587
11614	HELD_MAL_CC2	0,052	0,0518	0,0331	0,0346	0,0482	0,0373
11614	HELD_ALL_CC	0,0923	0,1151	0,0429	0,25	0,2653	0,2502
11614	HELD_ALL_HDL	0,0563	0,0558	0,0499	0,9149	1	0,9149
11631	HELD_MAL_ADR5ULN	, ,	0,0478	0,0304		0,0156	0,9149
11631	HELD_MAL_ADR3ULN	0,1371	0,1283		0,046	0,0572	
11637	HELD_FEM_LIP	0,0168	0,0155		0,0321	0,0372	0,051
11637	HELD_ALL_LIP	0,0303			0,0148		0,0317
11637	CVD_MAL .	0,0697		,	0,0248	0,0186	0,0149
11,637	CVD_ALL	0,0723	_1			0,0373	0,0272
11641	HELD_MAL_ADR	0,0142	0,0141		0,0254	0,0318	0,0262
11645	HELD_FEM_CC	0,0369	0,0544	0,0129	0,126	0,1468	0,1257
11646	HELD_FEM_LIP	0,0865	0,0344	0,0366	0,0456	0,0639	0,0454
11646	HELD_ALL_LIP	0,0788		0,0854	0,0359	0,0387	0,0356
11652	HELD_MAL_LIP	0,0788	0,077	0,078	0,0438	0,0453	0,0431
11727	HELD_ALL_ADRSULN		0,0402	0,0403	0,9398	. 1	0,9398
11727	HELD_MAL_ADR3ULN	.,	0,0169	0,001	0,0033	0,0029	0,0001
11727	HELD_MAL_ADRSULN	0,0139	0,0156	0,0019	0,0035	0,0042	0,0002
11727		0,0632	0,0556	0,0165	0,0205	0,0202	0,003
11727	HELD_ALL_ADR3ULN	0,0384	0,0373	0,0163	0,0076	0,0071	0,0036
	HELD_FEM_ADRSULN	0,1918	0,2611	0,0649	0,0728	0,128	0,0182
11728	HELD_ALL_ADR5ULN	0,1462	0,1458	0,095	0,0556	0,0654	0,0388
11914	HELD_MAL_ADR3ULN	0,2466	0,3289	0,2216	0,0257	0,0387	0,0248
11938	HELD_ALL_ADRIULN	0,0089	0,0095	0,0046	0,392	0,459	0,3897
11938	HELD_ALL_ADRSULN	0,0169	0,0157	0,0114	0,8154	0,8766	
	HELD_FEM_ADR3ULN	0,0449	0,0479	0,0352	0,6253		0,815
11950	HELD_MAL_ADR5ULN	0,0201	0,0516	0,0044		0,6469	0,6247
	FIFT P. A.C.	0,0154	0,0166	0,0044	0,0125	0,0113	0,0014
1950	77777	0,0516	0,0613	0,0496	0,0323	0,0548	0,0214
1951	CIPC W		0,0545		0,3586	0,4444	0,3582
1951	UELD		0,0235	0,0114	0,0236	0,0423	0,0037
		-,0239	0,0233	0,0107	0,0733	0,0868	0,0749

BAYSN				EGTYP	EALLEL	E, ALCEL	EALLE
12000			CE XPV	L RPV	L CPVAI	XPVAI	AND SHOOT IN THE CASE OF
12008		0,048	5 0,062	0,0449	0,0524	0,0663	0,048
12031	HELD_ALL_ADR3UL		8 0,002	4 0,0026	0,63	0,7148	0,630
12031	HELD_FEM_ADRSUL	N 0,004	6 0,003	9 0,0086	0,0566	0,0838	0,056
12031	HELD_ALL_ADR5UL	N 0,004	7 0,004	1 0,0086		0,0658	0,050
12031	HELD_FEM_ADR3UL	N 0,005	6 0,006	0,006	0,2925	0,3532	
12031	HELD_ALL_ADR	0,013	8 0,014	· ·		0,332	0,292
12031	HELD_FEM_ADR	0,014			0,1206		0,103
12032	HELD_FEM_UEFF	0,0304		_	0,0076	0,1247	0,120
12032	HELD_FEM_ADR	0,1261				0,0093	0,0078
12032	HELD ALL ADR	0,0928			0,0343	0,0448	0,031
12032	HELD_FEM_VEFF	0,0639			0,0359	0,0376	0,0341
12148	HELD_MAL_ADR5ULN	1 .	1 .,		0,0748	0,0929	0,0737
12148	HELD_MAL_ADR	0,0376		-	0,0087	0,0155	0,0126
12148	HELD_MAL_ADR3ULN		, , , , ,	0,0328	0,0142	0,0207	0,0139
12207	HELD_MAL_ADRSULN			0,085	0,0349	0,046	0,0398
12207	HELD_MAL_ADR	-	0,0036	0,002	0,6147	0,7792	0,6195
12207	HELD_MAL_ADR3ULN	0,003	0,0028	0,002	0,1131	0,1259	0,1125
12399			0,0181	0,0298	0,5888	0,6671	0,5919
12399	HELD_MAL_ADRSULN		0,0336	0,0287	0,0338	0,0497	0,0552
12399	HELD_MAL_ADR3ULN	0,0366	0,0602	0,0433	0,0568	0,0858	0,0714
	HELD_ALL_ADR	0,1174	0,109	0,1156	0,0393	0,0481	0,0386
12554	HELD_MAL_ADR	0,0489	0,0266	0,0384	0,0217	0,0303	0,0198
12554	HELD_FEM_VEFF	0,0785	0,0754	0,0774	0,0335	0,0365	0,0329
12851	HELD_FEM_ADR5ULN	0,0841	0,0704	0,087	0,0401	0,0635	0,0329
12851	HELD_MAL_ADR	0,0496	0,0509	0,0432	0,6573	0,6625	
13025	HELD_MAL_ADR3ULN	0,0572	0,0578	0,0424	0,8568	1	0,6573
13025	HELD_FEM_ADRSULN	0,0508	0,0491	0,0749	0,2494		0,8564
13191	HELD_ALL_CC	0,0795	0,0789	0,0666	0,0287	0,3182	0,2546
13192	HELD_MAL_ADR3ULN	0,0028	0,0047	0,0052		0,0329	0,0278
	HELD_MAL_ADRSULN	0,0306	0,0985	0,1047	0,2629	0,3274	0,2753
	HELD_ALL_ADR3ULN	0,0459	0,0411		0,6516	0,7437	0,6584
13192	HELD_MAL_ADR	0,0927	0,0909	0,0633	0,9559	1	0,9559
13193	HELD MAY			0,0428	0,7098	0,743	0,7097
		U,UULL	0,0038	0,0046	0,2596	0,3258	0,2719

BAYS		CTV	L XEV	LRPV	e picpyai	E ALLEI XPVAI	
13193	HELD_MAL_ADR5UL	N 0,022	7 0,088			·	Not the hand the little
13193	HELD_ALL_ADR3UL	N 0,037	5 0,034		{		
13338	HELD_FEM_UEFF	. 0,031	4 0,033			0,5935	0,9355
13338	HELD_FEM_VEFF	0,030	6 0,030		0,8319	0,8624	
13339	HELD_MAL_ADR	0,035	2 0,036	L	0,4768	0,5694	0,8319
13339	CVD_FEM	0,136	2 0,095				0,4767
13340	HELD_FEM_VEFF	0,015	8 0,0143	P.		0,0803	0,0465
13479	HELD_FEM_UEFF	0,106			1	0,0095	0,0072
13633	HELD_FEM_ADR3ULN	V 0,091	_1		0,0317	0,0364	0,0351
13633	HELD_FEM_ADR	0,1138				0,037	0,0361
13929	HELD_MAL_ADR5ULN				0,0387	0,0448	0,0384
14065	HELD_FEM_EFF	0,087			0,1262	0,2119	0,0423
14083	HELD_FEM_ADR	0,069	0,0657		0,0307	0,037	0,0303
14085	HELD_FEM_EFF	0,0345			0,0353	0,0459	0,034
14087	HELD FEM EFF	0,0509		4	0,1267	0,1326	0,126
14102	HELD MAL ADRSULN				0,1138	0,1184	0,1138
14102	HELD_FEM_EFF	0,1217			.0,8445	1	0,844
14103	HELD_FEM_EFF	0,003	0,0023	0,1207	0,0351	0,0391	0,035
14103	HELD_FEM_VEFF	0,0371	<u></u>	0,0004	0,0567	0,0623	0,0565
14103	HELD_FEM_UEFF	0,0605	0,0337	0,0117	0,495	0,5329	0,4948
14129	HELD_ALL_ADR3ULN	0,0384	0,0655	0,0291	0,0747	0,0807	0,076
14129	HELD_MAL_ADR3ULN	<u> </u>	0,0376	0,0479	0,1413	0,1647	0,1434
14326	HELD_FEM_EFF	0,0448	0,04	0,0567	0,3415	0,4056	0,3453
14503	HELD_ALL_ADRSULN	0,1463	0,1445	0,1434	0,0461	0,0471	0,0457
14503	HELD_ALL_ADR3ULN	0,0052	0,0046	0,0021	0,6567	0,7349	0,6547
14503	HELD_FEM_ADR5ULN	0,0046	0,0045	0,004	0,5974	0,6922	0,5986
14503	HELD_FEM_ADR3ULN	0,0136	0,0123	0,0063	0,9862	1	0,9862
14537	HELD_ALL_ADR	0,0203	0,0189	0,0179	0,482	0,5051	0,4834
4537		0,0148	0,0153	0,0133	0,0049	0,0053	0,0048
5915	HELD_FEM_ADR .	0,0395	0,0398	0,0332	0,0288	0,0309	0,0284
5915	HELD_FEM_ADR	0,0018	0,0013	0,0012	0,6403	0,6575	0,6405
	HELD_ALL_ADR	0,0037	0,0031	0,0029	0,4718	0,5008	0,4719
	HELD_ALL_ADRIULN	0,1292	0,1365	0,0778	0,0267	0,0357	0,021

	COMPARISON COMPARISON	GEVA	L GRYP	C VE LREVA	ALLE		CALERIA
19289	HELD_MAL_CC	0,0256		The second of th	Contract States of States	持一种的政治	988年(建立学会)
19289	HELD_ALL_CC	0,0392					0,1642
19289	HELD_MAL_LIP	0,0974			0,0989	0,1133	0,095
36958	HELD_MAL_ADR3ULN	1 1	1 ' ===	0,0855		0,0689	0,0515
37158	HELD_ALL_ADR	0,0266			0,0926	0,1218	0,0274
37158	HELD_FEM_ADR	0,0547		0,0248	0,0076	0,0078	0,0074
37160	HELD_FEM_UEFF	0,0494		0,047	0,0328	0,0384	0,0323
37412	HELD_FEM_ADRSULN	1		0,0291	0,0206	0,0238	0,0215
37412	HELD_ALL_ADRSULN	1 -		. 0,0228	0,0901	0,1029	0,0965
37412	HELD_FEM_ADR3ULN	1 ,		0,0443	0,1444	0,1838	0,1518
37457	CVD_ALL			0,1428	0,0436	0,0523	0,0457
37457	CVD_FEM	0,006	0,0043	0,0045	0,0004	0,0006	0,0005
37457	CVD_MAL	0,0618	0,0475	0,0371	0,0084	0,0138	0,0049
37704	HELD_MAL_ADRSULN	0,1106	. 0,1397	0,1478	0,0425	0,0646	0,0633
38959	CVD_ALL	ļ	0,1304	0,041	0,0096	0,1304	0,0423
38959	<u> </u>	0,0357	0,0284	0,0234	0,7204	0,8145	0,7186
39292	HELD_FEM_EFF	0,0937	0,0903	0,0433	0,1155	0,1245	0,1149
39292	HELD_FEM_ADR5ULN	0,0461	0,0797	0,1143	0,0295	0,0406	0,0445
	HELD_ALL_ADRSULN	0,2107	0,197	0,2673	0,0487	0,0566	0,0656
39698	HELD_MAL_ADRJULN	0,0549	0,0575	0,0339	0,1964	0,2316	0,1955
39756	HELD_FEM_ADR3ULN	0,1838	0,1894	0,1779	0,0494	0,069	0,0449
39951	HELD_MAL_ADR	0,0126	0,0133	0,0027	0,1824	0,227	0,1816
39951	HELD_ALL_ADR	0,0036	0,0033	0,0031	0,7179	0,7614	0,7178
39951	HELD_FEM_ADR	0,0243	0,023	0,0233	0,0941	0,102	0,0932
39951	HELD_FEM_ADR5ULN	0,0673	0,0646	0,0583	0,0366	0,0423	0,0421
40466	HELD_FEM_EFF	0,0024	0,002	0,0009	0,0045	0,0058	0,0044
40466	HELD_FEM_UEFF	0,0802	0,0728	0,0265	0,0419	0,0518	0,0382
40466	HELD_FEM_VEFF	0,0511	0,0458	0,0386	0,0313	0,0339	0,0309
44442	HELD_MAL_ADR5ULN	0,0836	0,079	0,0743	0,0364	0,0585	0,0418
55504	HELD_MAL_ADR	0,0719	0,0735	0,0691	0,0286	0,0345	
55542	HELD_FEM_ADR	0,0351	0,0377	0,0327	0,0223	0,0343	0,0284
55670	HELD_FEM_VEFF		0,0252	0,0172	0,0215		0,0221
55736	LYCER ATT		0,0583	0,0098	0,0215	0.03	0,0208
				3,5000	0,0203	0,0356	0,0023

	SNE		DESCRIPTION OF				ALL	ELE AL	LEL	E ALL
557	36 HPLD MAL ADD					<b>LPV</b> A	C CPV		VAL	
557		SULN			87 0	,0194	0,09	200 mm. 2. 150 4.3.	1202	0,02
5574					065 0	,1534	0,11		2053	0,038
5581	NTAU_ADR		4		008 0,	1412	0,13		2136	0,046
5584	· LED_ADRO		0,093		76 0,	0867	0,02		248	0,043
5584			0,020	_   -,	42 0,	0254	0,012		138	
5584	THE MURI		0,095	_   ',	88 0,	0453	0,043		619	0,012
55923	- LED TENT OF		0,137	8 0,14	2 0,	1358	0,04		588	0,037
55923			0,0587	7 0,05	8 0,0	556	0,019		224	0,045
55945	ADR3		0,0606	0,056	52 0,0	659	0,021			0,018
55945			0,0125	0,010		112	0,003			0,0222
		,	0,0381	0,037		442	0,0127			0,003
55945			0,0809	0,080	_ 1 .	·	0,0292			0,0137
56007	HELD_MAL_ADR3U		0,0308	0,029			0,1915			0,029
56007	HELD_MAL_ADRSU		0,139	0,147	_L "					0,1828
56011	HELD_ALL_ADRSULN HELD_FEM_UEFF		0,1056	0,2178			0,2654	-		0,2514
56104			0,0155	0,0153	1 -,	/	0,1135			0,0343
56113	HELD_ALL_ADR5UI	LN	0,0186	0,0163	1 .	1	0,0164		_ 1	0,0166
56113	HELD_ALL_ADR3UI	NO	,0285	0,029	0,02	!	0,0347	0,038	37	0,0352
56.113	HELD_FEM_ADR5UI		,0402	0,0472	_L		0,3219	0,379	4	0,3228
56113	HELD_FEM_ADR3UL		.0416	0,0401		!	0.036	0,049	8	0,0358
56636	HELD_FEM_ADR		0108	0,0106	0,043		0,1311	0,151	9	0,1314
56636	HELD_FEM_ADR3UL		0227	0,0223		_ 1	0,5577	0,616	9	0,5576
56636	HELD_FEM_ADR5UL			0,0247	0,021		0,7019	0,753	2	0,7016
56666	HELD_MAL_ADR3UL			0,3446	0,027		0,8077	0,8498	3	0,8079
56666	HELD_MAL_ADRSUL		3794	0,418	0,076		0,0154	0,0133	1	0,0018
6666	HELD_MAL_ADR		717	0,119	0,191		0,0556	0,0716		0,0122
6667	HELD_FEM_EFF				0,136		0,0173	0,0265	1	0,0154
6667	HELD_MAL_ADRIULN			0,0372	0,0356		0,0134	0,014		0,0133
6667	HELD_FEM_ADRIULN	0,1		0,4124	0,2471	L`	0,0382	0,0579		),0311
6780	HELD_FEM_ADR3ULN			0,1267	0,1124		,0483	0,0586		,0492
5780	HELD FEM ADR			,0159	0,008	1	0,012	0,0164		,0117
780	HELD_ALL_ADRIULN	0,02	===	,0214	0,0192		0,012	-0,0154-		01-18
	ZADIGOUN	0,02	69 0	.0274	0,019	0	,0143	0,0182		0141

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	<b>医胚层的 经股份的 医</b>	100	TTT 40'4 E. 241.23 Ct	TRP/AL	CRYAL	XPVAL	ERPVAL
56780	HELD_ALL_ADR	0,0842	0,0843	0,0808	0,0435	0,0453	0,0433
56876	HELD_FEM_UEFF	0,0372	0,0266	0,0308	0,0169	0,0232	0,0141
56876	HELD_FEM_EFF	0,0424	0,0386	0,0418	0,0166	0,0177	0,0163
56876	HELD_FEM_VEFF	0,0713	0,0569	0,0692	0,0196	0,0216	0,0192
56978	HELD_ALL_ADR5ULN	0,0719	0,0767	0,0535	0,0154	0,0156	0,0118
57000	HELD_FEM_VEFF	0,0174	0,0176	0,0169	0,3734	0,4158	0,3731
57000	HELD_FEM_UEFF	0,0415	0,0406	0,0369	0,858	0,8914	0,8579
57000	CVD_ALL .	0,0418	0,0488	0,0445	0,0607	0,0713	0,0637
57000	CVD_MAL	0,0441	0,0754	0,0552	0,1657	0,2666	0,1782
57313	HELD_FEM_UEFF	0,034	0,0307	0,0344	0,1193	0,15	0,1201
57734	HELD_FEM_ADR3ULN	0,1496	0,1859	0,1593	0,0475	0,0622	0,0534
. 57837	HELD_MAL_ADR3ULN	0,1875	0,2505	0,1226	0,0606	0,0663	0,0405
57853	HELD_FEM_EFF	0,0026	0,0022	0,0012	0,0086	0,0107	0,0084
57853	HELD_FEM_UEFF	0,0504	0,0448	0,0138	0,0301	0,0444	0,0274
57853	HELD_FEM_VEFF	0,042	0,0386	0,0288	0,0505	0,0562	0,0501
57854	HELD_FEM_EFF	0,0212	0,0209	0,0157	0,0665	0,0761	0,0663
57854	HELD_FEM_UEFF	0,0736	0,0661	0,0242	0,0496	0,068	0,0464
57854	HELD_MAL_ADRIULN	0,1957	0,2011	0,1232	0,0634	0,0859	0,0467
58295	HELD_MAL_ADR	0,0215	0,0221	0,0192	0,0596	0,0793	0,0593
58402	HELD_MAL_ADR3ULN	0,253	0,3601	0,2207	0,0277	0,0317	0,0255
58407	HELD_FEM_VEFF	0,009	0,0089	0,0086	0,6756	0,7344	0,6756
58407	HELD_FEM_UEFF	0,0269	0,0254	0,019	0,1833	0,1983	0.1819
58440	HELD_FEM_UEFF	0,1021	0,1012	0,1022	0,0294	0,0358	0,0305
58525	HELD_FEM_ADR	0,0008	0,0004	0,0004	0,0002	0,0003	0,0001
58525	HELD_FEM_ADR3ULN	0,0005	0,0002	0,0008	0,0002	0,0006	0,0005
58525	HELD_FEM_ADRSULN	0,0002	0,0005	0,0011	0,0009	0,0042	0,0034
58525	HELD_ALL_ADR	0,0309	0,0274	0,0284	0,0041	0,005	0,0037
38525	HELD_ALL_ADRSULN	0,0115	0,0352	0,0209	0,0263	0,0423	0,0037
58525	HELD_ALL_ADR3ULN	0,0304	0,0391	0,0408	0,0158	0,0198	0,0412
58533	HELD_FEM_ADR	0,0132	0,0076	0,011	0,0024	0,0138	
58533	HELD_FEM_ADR3ULN	0,0373	0,0325	0,0534	0,0101	0,0033	0,0019
<u>5853</u> 3	HELD_FEM_ADRSULN	0,0255	0,0368	0,0556	0,0387		0,0155
·				-,,,,,,,,	0,0307	0,0613	0,0658

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59572		PROPRIETARE AND	3 high the or the 25	ERPVAE	CPVAL	XPVAL	LRPVAL
58533	HELD_ALL_ADR	0,1948	0,2046	0,1921	0,0446	0,0584	0,0438
58544	HELD_MAL_ADRSULN		0,1955	0,0875	0,0754	0,1197	0,02
58716	HELD_MAL_ADR3ULN		0,0288	0,011	0,0012	0,0018	0,0003
58716	HELD_MAL_ADR5ULN	0,1918	0,256	0,1602	0,0649	0,0886	0,047
58736	HELD_FEM_EFF	0,0378	0,0385	0,0374	0,0117	0,0131	0,0117
58808	HELD_FEM_ADR	0,0754	0,076	0,0739	0,0276	0,0333	0,0275
58809	HELD_MAL_ADR5ULN	0,1338	0,1368	0,0404	0,0454	0,0777	0,0088
58809	HELD_ALL_ADR3ULN	0,0117	0,011	0,0202	0,0915	0,1137	0,0090
58809	HELD_MAL_ADR3ULN	0,0206	0,0207	0,0247	0,2401	0,3238	0,253
58809	HELD_FEM_UEFF	0,1023	0,1072	0,0586	0,0482	0,0528	0,0446
58886	HELD_FEM_ADR3ULN	0,0432	0,0444	0,0387	0,0115	0,0145	ļ <u>.</u>
58886	HELD_ALL_ADR3ULN	0,0611	0,0627	0,0549	0,0171	0,0143	0,0107
58886	HELD_ALL_ADR5ULN	0,1212	0,1272	0,097	0,0433		0,0168
58926	HELD_MAL_ADR3ULN	0,0186	0,0222	0,0152	0,0433	0,049	0,0427
58926	HELD_ALL_ADRSULN	0,0504	0,0525	0,0172		0,005	0,0036
58926	CVD_FEM	0,0461	0,0455	0,0470	0,0108	0,0121	0,0117
58926	HELD_MAL_ADR5ULN	0,1263	0,1409		0,7899	0,8184	0,7899
58968	HELD_ALL_ADRSULN	0,0212		0,1002	0,0427	0,0517	0,0487
58968	HELD_MAL_ADR3ULN	0,0412	0,0248	0,0199	0,0023	0,003	0,003
58968	HELD_ALL_ADR3ULN		0,0375	0,0377	0,0067	0,0098	0,0085
	HELD_FEM_ADRSULN	0,1321	0,1309	0,1338	0,0208	0,028	0,0226
		0,1447	0,1579	0,1408	0,0233	0,0292	0,0261
	HELD_ALL_ADRSULN	0,0341	0,0303	0,0449	0,0085	0,0129	0,0104
	HELD_MAL_ADRSULN	0,0156	0,0224	0,0114	0,0006	0,0008	0,0003
	HELD_MAL_ADR3ULN	0,0577	0,0875	0,0558	0,0073	0,009	0,0068
59236	HELD_ALL_ADR	0,0163	0,0158	0,0148	0,0638	0,077	0,0636
	HELD_ALL_ADR3ULN	0,0152	0,0151	0,017	0,3664	0,3858	0,3685
59236	HELD_FEM_ADR	0,0242	0,0266	0,0221	0,0693	0,0722	0,0689
59237	HELD_FEM_VEFF	0,021	0,0197	0,0205	0,9766	1	0,9766
59237	HELD_FEM_EFF	0,0278	0,0283	0,0273	0,5742	0,6002	0,5742
59267	HELD_FEM_UEFF	0,0007	0,0006	0,0005	0,0035	0,0042	
59352	HELD MAL ADR	0,0234	0,0233	0,0219	0,6204		0,0036
59352	HELD_ALL_ADR	0,0427	0,0412	0,0406	0,8742	0,6787	0,6203
<u>-</u>		L		-,0-,00	V,0742	0,925	0,8742

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59363	CVD_MAL	0,0678	0,0736	0,0797	0,0336	0,0422	0,0351
59368	HELD_FEM_ADR	0,0119	0,0127	0,0096	0,0049	0,0053	0,0048
59371	HELD_FEM_VEFF	0,0024	0,0022	0,0021	0,1509	0,1694	0,1508
59371	HELD_FEM_UEFF	0,0098	0,0099	0,0092	0,2681	0,286	0,2686
59372	HELD_MAL_ADR	0,1687	0,1722	0,1609	0,0282	0,042	0,0273
59372	HELD_MAL_ADR3ULN	0,22	0,2638	- 0,2592	0,0467	0,0804	0,0599
59443	HELD_ALL_ADRSULN	0,0027	0,0031	0,0018	0,366	0,4699	0,3621
59443	HELD_MAL_ADR5ULN	0,0416	0,036	0,0368	0,877	1	0,877
900080	HELD_FEM_ADR3ULN	0,0248	0,0243	0,0334	0,0078	0,0122	0,011
900080	HELD_FEM_ADRSULN	0,0307	0,0334	0,0528	0,0422	0,0571	0,0639
. 900102	HELD_FEM_UEFF	0,0079	0,0078	0,008	0,0043	0,0057	0,0041
900102	HELD_FEM_VEFF	0,0423	0,0413	0,0416	0,0163	0,0185	0,0162
900111	HELD_FEM_UEFF	0,022	0,0232	0,0222	0,0107	0,012	0,0103
900111	HELD_FEM_VEFF	0,0524	0,0496	0,0516	0,0293	0,0351	0,0292
900117	HELD_MAL_LIP	0,049	0,0534	0,022	0,0073	0,0136	0,0043
900118	HELD_FEM_EFF	0,0013	0,0008	0,001	0,0001	0,0002	0,0001
900118	HELD_FEM_VEFF	0,1013	0,0874	0,0978	0,0214	0,0303	0,0206
900118	HELD_FEM_ADRSULN	0,0424	0,0506	0,0251	0,8579	1	0,8561
900118	HELD_ALL_ADR5ULN	0,0702	0,0623	0,0401	0,653	0,7517	0,6608
900120	HELD_FEM_EFF	0,0101	0,0092	0,007	0,0095	0,0109	0,0093
900121	HELD_FEM_EFF	0,0944	0,0944	0,0922	0,0477	0,0488	0,0476
900123	HELD_ALL_ADR	0,0402	0,0568	0,0164	0,041	0,0576	0,0168
900123	HELD_FEM_ADR	0,0678	0,1074	0,0341	0,0695	0,1089	0,0349
900124	HELD_FEM_EFF	0,0185	0,0181	0,0177	0,0602	0,0663	0,0601
900132	HELD_FEM_ADR	0,0215	0,0178	0,0068	0,2283	0,2679	0,2288
900144	CVD_FEM	0,0319	0,0744	0,0093	0,0361	0,0813	0,0104
900144	HELD_ALL_ADRSULN	0,1356	0,2119	0,0476	0,1425	0,2202	0,0497
900145	CVD_FEM	0,0702	0,0367	0,0231	0,4142	0,4698	0,4044
900145	HELD_ALL_ADRSULN	0,1364	0,2117	0,0481	0,1436	0,2203	0,0504
900146	HELD_FEM_ADR5ULN	0,0096	0,017	0,0195	0,0366	0,0413	0,0447
900146	HELD_FEM_CC	0,0751	0,0844	0,0429	0,4385	0,4606	0,4405
900146	HELD_MAL_ADR	0,1074	0,1347	0,0497	0,2672	0,3098	0,2671

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000147		PLANTAL CONTRACTOR	1 10 15 15 15 15	TRPVAL	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	XPVAL	LRPVAL
900147	HELD_ALL_ADR3ULN	0,0572	0,0567	0,0416	0,0133	0,015	0,0104
900147	HELD_FEM_ADR3ULN	0,0435	0,0527	0,0381	0,0166	0,0182	0,0127
900196	HELD_MAL_LIP	0,04	0,0376	0,0365	0,0037	0,0057	0,0039
900196	HELD_FEM_LIP	0,0183	0,019	0,0214	0,0168	0,0301	0,0136
900196	HELD_FEM_ADR3ULN	0,0672	0,0693	0,022	0,0238	0,0276	0,0198
900196	CVD_FEM	0,0398	0,0432	0,0293	1	1	1
900196	CVD_ALL	0,0617	0,0655	0,0425	0,1649	0,2139	0,1618
900200	CVD_FEM	0,0865	0,0948	0,0822	0,0359	0,0545	0,0381
900204	HELD_FEM_EFF	0,0051	0,0054	0,005	0,0195	0,0204	0,0194
900205	HELD_FEM_EFF	0,0128	0,0126	0,0126	0,0746	0,0753	0,0745
900205	CVD_MAL	0,0881	0,0873	0,0279	0,0497	0,0672	0,045
900223	HELD_FEM_ADR	0,1823	0,2018	0,1522	0,0357	0,0826	0,0327
900225	HELD_ALL_ADR5ULN	0,0532	0,0765	0,011	0,0615	0,0864	0,0125
900225	HELD_MAL_ADR3ULN	0,0804	0,108	0,0242	0,0926	0,1218	0,0274
900227	HELD_FEM_ADRIULN	0,076	0,0933	0,0368	0,0271	0,031	0,0108
900233	HELD_FEM_ADRSULN	0,0314	0,0303	0,024	0,3185	0,3387	0,3136
900236	HELD_FEM_ADR3ULN	0,0378	0,0275	0,0387	0,0494	0,064	0,0568
900236	HELD_MAL_ADRSULN	0,2375	0,2927	0,0919	0,0994	0,13	0,0289
900241	HELD_FEM_EFF	0,0225	0,0223	0,0219	0,6377	0,6538	0,6376
900242	HELD_ALL_ADRSULN	0,0164	0,0165	0,0012	0,0015	0,0017	0
900242	HELD_ALL_ADR3ULN	0,0158	0,0151	0,0031	0,0007	0,0006	0,0002
900242	HELD_FEM_ADR5ULN	0,0257	0,0467	0,0032	0,0088	0,0105	0,0007
900242	HELD_MAL_ADRJULN	0,1963	0,3073	0,0673	0,0132	0,0144	0,0014
900242	HELD_FEM_ADR	0,0219	0,0117	0,0142	0,006	0,0067	0,0053
900242	HELD_FEM_ADR3ULN	0,0542	0,0556	0,0305	0,0161	0,0247	1000,0
900242	HELD_ALL_ADR	0,0373	0,0359	0,0352	0,0146	0,0152	0,0142
900242	HELD_MAL_ADRSULN	0,416	0,4311	0,2189	0,0691	0,1332	0,0142

<u>Table 6a</u> Correlation of genotypes of PA SNPs to relative risk

For diagnostic conclusions to be drawn from genotyping a particular patient we calculated the relative risk RR1, RR2, RR3 for the three possible genotypes of each SNP. Given the genotype frequencies as

	gtype1	gtype2	gtype3
case	NII	`N12	N13
control	N21	N22	N23

we calculate

5

$$RR1 = \frac{N11}{N21} / \frac{N12 + N13}{N22 + N23}$$

$$RR2 = \frac{N12}{N22} / \frac{N11 + N13}{N21 + N23}$$

$$RR3 = \frac{N13}{N23} / \frac{N11 + N12}{N21 + N22}$$

Here, the case and control populations represent any case-control-group pair, or bad(case)-good(control)-group pair, respectively (due to their increased response to statins, 'high responders' are treated as a case cohort, whereas 'low responders' are treated as the respective control cohort). A value RR1>1, RR2>1, and RR3>1 indicates an increased risk for individuals carrying genotype 1, genotype 2, and genotype 3, respectively. For example, RR1=3 indicates a 3-fold risk of an individual carrying genotype 1 as compared to individuals carrying genotype 2 or 3 (a detailed description of relative risk calculation and statistics can be found in (Biostatistics, L. D. Fisher and G. van Belle, Wiley Interscience 1993)). The baySNP number refers to an internal numbering of the PA SNPs and can be found in the sequence listing. null:

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In cases where a relative risk is not given in the table (three times zero or null) the informative genotype can be drawn from the right part of the table where the frequencies of genotypes are given in the cases and control cohorts. For example BaySNP 3360 gave the following results:

BAYSNE	COVID	RISONE	ST PP.		GEYPE3	RR	RR2	RR3
	HELD_MAL		GG	GI.	TT	null	0	0.

FOLA	IQ2A	TO WE	TOLK.	EQ2_B	FQ3_B
10	0	0	50	22	1

It can be concluded that a GT or TT genotype is only present in the control cohort; these genotypes are somehow protective against ADR. An analogous proceeding can be used to determine protective alleles if no relative risk is given (table 6b).

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d Conda		6	2 2	2 3	77	77	2   2	745	3 -	5   5	27 22	5	0	8.1	15	15	29	20	67	97	ė.	62	62	30	,
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RREIRRA	62,0	0,75	0.81	1,6	. 90	1,45	1,82	1,14	1,62	0,86	2,18	1,37	1.39		8	0,72	0,86	0,84	0,45	0.24	151	1 8	7,17	1,84	
RRE	1,26	1,33	133	0,63	0,94	69,0	0,55	0,88	0,62	1,16	0,46	0,73	0.72	- -		1,38	1,16	1.2	2,22	4,16				0,54	
COMPARISON	HELD FEM LIP	HELD_ALL_ADR3ULN	HELD_ALL_LIP	HELD_ALL_CC	HELD MAL HDL	HELD_FEM_CC	HELD_MAL_CC	HELD MAL LIP2	HELD FEM CC	HELD_MAL_LIP2	HELD_MAL_ADRSULN	HELD_ALL_ADRSULN	HELD ALL ADRIULN	+-	-+	HELD_MAL_ADR3ULN   1	HELD_ALL_ADRSULN 1	HELD_ALL_ADR	HELD_ALL_ADR3ULN 2	HELD_MAL_ADR3ULN 4		-}-	-+	HELD_MAL_ADR3ULN 0,	
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RR	0,82	1,13	1,47	8,0	0,78	冒	ig	1,57	6,2	59'0	0,47	0,52	8.0	69'0	0,82	1,58	18,0	1,28	12'0	1,28	1,52 0	1,15 0	
COMPARISON	CVD_ALL	CVD_ALL	HELD_FEM_CC	· CVD_ALL	HELD_FEM_ADR	HELD_ALL_LIP	HELD_FEM_LIP	CVD_MAL	HELD_MAL_HDL	HELD_ALL_CC	HELD_MAL_CC	HELD_MAL_LIP	CVD_ALL	HELD FEM CC	. CVD_ALL	HELD_ALL_HDL	HELD_FEM_LIP 0	HELD_MAL_ADRSULN	HELD_MAL_CC2	HELD_ALL_LIP 1	HELD_ALL_CC 1	. CVD_MAL 1	
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COMPARISON	HELD_MAL_ADR3ULN	HELD FEM EFF	CVD_MAL .	HELD MAL ADRSULN	HELD_ALL_CC	HELD_FEM_CC	HELD FEM VEFF	HELD_MAL_ADR	HELD_ALL_LIP	HELD_ALL_ADR3ULN	HELD_ALL_ADRSULN	HELD_MAL_ADRSULN	HELD_FEM_ADR3ULN 2	HELD MAL ADRIULN 4		HELD_FEM_LIP 1	HELD_ALL_LIP 1	HELD_ALL_ADR 1,	HELD_FEM_LIP 0,	HELD_FEM_LIP 1,	HELD FEM_CC 1	HELD_ALL_CC 1,	
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SIZE	14	45	19	39	624	<b>8</b> .	12	43	237	46	119	16	53	58	6	30	69	30	132	16	47	28	1
III	2,4	1,38	0,45	9,0	0,88	69,0	1,75	0,46	0,77	0,62	0,74	0,26	0,73	89'0	2,7	2,1	0,14	II DIE	0,46	Ind	0,34	1,35	-
B	0,42	0,73	2,22	1,68	==	1,46	0,57	2,15	13	1,61	1,35	3,89	1,37	1,47	0,37	0,65	7,27. 0		2,19 0	0	2,97	0,74 1,	1
COMPARISON	HELD MAL CC	HELD_ALL_CC	HELD MAL HDL	HELD_ALL_FIDI	HELD_ALL_LIP2	HELD FEM LIP	HELD_MAL_LP	HBLD_FEM_UEFF	HELD_FEM_EFF	HELD_MAL_ADR	HELD_FEM_VEFF	HELD_MAL_ADR3ULN 3	HELD FEM UEFF 1	HELD MAL ADR 1	HELD_MAL_ADRSULN 0	HELD_FEM_ADR3ULN 0	HELD_FEM_ADR 7,	HELD FEM ADR3ULN	HELD_ALL_ADR 2,	HELD_FEM_ADRSULN	HELD_ALL_ADR3ULN 2,	HELD_FEM_LIP 0,	
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IN	1,25	2,17	0,42	1,55	0,58	0,28	2,41	8,0	0,64	65,0	Ε'1	1,36	0.62	2	1	0,65	1,1	1,26	15,1	60,0	0,12	1,04	15,1	$\dashv$
RH	0,8	0,46	2,4	0,64	17.1	3,58	0,42	1,24	15,	1,68	60	0,74	1,62		<del> -</del>	\$. 2	16'0	0,79	0,77	11,29 0	8,33 0	0,96	0,77 1,	-{
COMPARISON	HELD_ALL_LP	· HELD_MAL_CC	CVD_FEM	HELD_FEM_CC	HELD_MAL_CC	HELD_MAL_LIP	HELD MAL CC	HELD_MAL_ADR	HELD_MAL_ADRSULN	HELD_MAL_ADR3ULN	HELD_FEM_BFF	CVD_MAL 0	HELD_ALL_CC		1		HELD_ALL_LIP2 0	HELD_ALL_LP2 0	HELD_FEM_UEFF 0	HELD_ALL_CC 11	HELD_FEM_CC 8,	HELD_FEM_LIP2 0,	HELD_FEM_ADR 0,	1
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FREOZ B	26	235	156	88	13	100	53	0	5	53	17	24	17	0	0	0	17	10	62	7	26	103	
IIR O FB	162	333	134	99	49	116	231	120	31	49	17	156	7.1	126	99	99	17	20	84	141	46	191	1
SIZEB	128	284	145	11	31	108	142	99	81	51	44	8.	4	63	Ŕ	33	17	15	57	74	36	132	1
FREO'TA SIZE B	121	211	119	44	2	68	49	-	-	33	4	1	1	10	7	3	14	13	30	17	9	49	
RRO SIZE A GREOTER	147	331	163	22	32	125	253	17	55	. 25	0	35	23	190	129	19	32 .	=	76	16	30	47	
Y azis	134	271	141	22	17	107	151	6	28	. 45	7	82	12	100	88	32	23	12	53	54	82	48	-
MR.	1,18	0,95	0,79	89'0	0,34	16'0	0,92	8,06	0,26	17,0	Hon	0,22	0,23	99,1	1,47	2,08	69'0	1,59	69'0	1,8,1	0,47	1,43	
	0,85	1,05	1,27	1,48	2,96	13	1,09	0,12	<del>ي</del> عور	4,1	0	4,58	4,4	9,0	89.0	0,48	1,45	0,63	1,46	0,55	2,11	200	
E CONTAINSONE	HELD_ALL_ADR	HELD FIM EFF	HELD_REM_VEFF	HELD_FEM_UEFF	HELD_FEM_ADR3ULN	HELD_FEM_VEFF	HELD_FBM_VEFF	HELD_MAL_ADRSULN	HELD_FEM_CC	HELD_MAL_ADR	HELD_MAL_ADRSULN	HELD_ALL_ADRSULN	HELD_MAL_ADR3ULN	CVD_ALL	CVD_MAL	CVD_FEM	HELD_MAI_CC2	HELD_FEM_HDL	HELD_FEM_UEFF	HELD_FEM_UEFF	HELD MAL LIP	HELD_ALL_ADR3ULN	
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FERROZ A	72	28	28	132	7	. 61	78	46	16	14	37	83	31	14	37	83	00	86	0	14		68
ARCHROS SIZE A CREGICA	72	24	114	808	11	7.1	89	162	36	20	87	183	63	20	85	181	34	474	79	20	15	113
SIZE	2	92	12	320	12	45	48	104	26	41.	29	133	47	12	19	132 .	97	286	<u>s</u>	17	6	io.
THE STATE OF	1,7	1,65	0,85	0,84	2,15	0,7	1,5	18,0	1,71	2,34	1,35	1,23	4,	2,34	1,37	1,22	99'0	1,17	120	1,62	13.	0,83
RIE	0,79	19,0	1,18	1,19	0,47	1,43	29,0	1,24	65,0	0,43	0,74	0,82	69,0	0,43	0,73	0,82	1,52	0,85	1,44		0,76	1,2
DEALE CONTRAISON	HELD_FEM_ADR	HELD_ALL_ADRSULN	CVD_ALL	HELD_FEM_LIP2	HBLD_MAL_CC	HELD_MAL_CC2	HELD_ALL_ADR3ULN	HELD_ALL_CC2	HELD_ALL_ADRSULN	HELD_MAL_ADR3ULN	HELD_MAL_ADR	HBLD_ALL_ADR	HELD_ALL_ADR3ULN	HELD_MAL_ADR3ULN	HELD_MAL_ADR	HELD_ALL_ADR	HELD_ALL_ADRSULN	HELD FEM EFF	HELD MAL LIP	HELD_MAL_LP	HELD_MAL_ADRSULN (	HBLD_ALL_CC2
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Surris	34	59	59,	18	38	31	128	69	69	128	69	128	128	82	70	128	8	59	21	34	62	22	
HREO? A SIZE B	.138	36	5	2	15	17	45	33	21	30	78	135	44	32	20	28	6	54	35	33	78	6	
SIZE A EREO K	0	88	11	26	75	7	-15	29	13	22	89	135	52	30	14	23	27	89	. 25	25	96	77	
MIS	69	62	æ	4	45	12	48	31	17	26	73	135	48	31	17	56	18	19	30	32	87	18	
RRO	i i	1,19	1,51	0,25	19'0	2,21	1;1	1,28	1,77	1,62	1,2	1,14	1,08	1,28	1,68	15,1	0,47	0,81	1,4	1,66	0,82	0,47	1
RR	0	0,84	99'0	3,98	1,48	0,45	8	0,78	95,0	79,0	9,84	88,0	6,93	0,78	9,0	99,0	2,11	1,24	17,0	9,0	1,21	2,11	İ
URZ COMPARISON	CVD_MAL	HELD_MAL_ADR	HELD MAL ADRSULN	HELD_MAL_CC	HELD_ALL_CC	HELD_MAL_LIP	HELD_ALL_ADR3ULN	HELD_FEM_ADR3ULN	HELD_FEM_ADRSULN	HELD_ALL_ADRSULN	HELD FEM ADR	HELD_ALL_ADR	HELD_ALL_ADR3ULN	HELD_FEM_ADR3ULN	HELD_FEM_ADRSULN	HELD_ALL_ADRSULN	HELD_MAL_LIP	HELD_MAL_ADR	HELD_FEM_CC	CVD_FEM	HELD_ALL_CC2.	HELD_MAL_HDL	
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FREOISA	ಜ	5	46	2		911	24	01	757		2 2	551	53	42	27	98	2		88	26	12		5	73	15	37
	9 9	37	30		,	2	16	6	159	ដ	22	;	10	25	15	24	5	00	8	5	33	1 4	2	50	<b>60</b>	22
	0,75	7,0	1.6	- 1	10,	1,21	1,87	2,35	87	0 67	2	:	2,0	0,47	0,25	0.53		8,73	0,84	0,36	0.67	.   6	;	<u> </u>	0,18	0,48
والمبارز	الگر!	1,43	0,63	27.0	2,	0,82	0,53	0,42	0.77				-	2,13	4,08	1.88	+	2 7 'n	1,19	2,75 0	1,49	<del></del>			5,56 0,	÷
HEID ALL TIB	יום שתייוי	HELD_MAL_CC2	HELD_FEM_ADR3ULN	HELD MAL ADRSHIN	Control of the contro	nell_rem_ADR	HELD_FEM_ADRSULN	HELD_MAL_ADRSULN	HELD_FEM_VEFF	1	监	72	N'TO CALLE	ADRSULN	HELD FEM ADRSULN 4	HELD ALL ADRSULN	1		HELD_FEM_ADR 1	HELD_FEM_ADRSULN 2	HELD_MAL_ADR 1,	Z	-	$\dashv$	WAL ADRSULN	HELD_ALL_ADRSULN   2,07
T		L	Ą	Y	4	•	Ą	4	1	0	၁	7	Ę	1	<b>-</b>	Ŧ	F	1	ပ	<del>ر</del> ن	O	U U	F	\ \ \ \	1	<b>₹</b>
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5019	60.00	Sinc	5165	5165	5165	6166	2103	5278	. 5287	5320	5324	5373	5373	3263	CICC	5375	5376	4177	1100	2377	5517	5518	5564	5569	2560	

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IRRO2 B	92	. 83	92	53	122	91	6	28	33	63	20	43	20	70	55	22	75	37	9	15	7	10
FREQUE	126	65	126	65	142	22	21	30	83	193	112	205	112	112	89	72	17.1	62 .	30	99	29	130
SIZE	109	\$3	109	59	132	16	51	29	28	128	99	124	99	99	72	89	126	85	. 81	6	37	70
FREQUE	54	40	28	20	.32	22	14	38	40	188	-	13	39	81	20	4	42	. 19	28	7	15	27
maligne state of integer of statem are of the configuration of the confi	34	. 81	91	10	20	12	14	78	. 9 <i>t</i>	177	21	33	105	42	54	82	52 .	İŞ	0	. 83	55	191
W HINS	44	. 55	22	- 15	26	12	14	. S8	58	129	16	23	72	30	52	8	47	17	4	45	35	75
RRC	1,74	1,98	2,07	2,05	1,68	29,1	1,52	8,0	1,15	1,18	2,25	1,67	1,37	1,74	1,26	0,77	1,58	2,13	12	0,57	15,1	1,3
RRI	0,57	0,5	0,48	0,49	0,59	19'0	99,0	1,25	0,87	0,85	24,0	9,0	0,73	0,58	0,79	1,31	0,63	0,47	0	1,76	99,0	0,77
COMPARISON	HELD_ALL_ADR3ULN	HELD_FEM_ADR3ULN	HELD_ALL_ADRSULN	HELD_FEM_ADRSULN	HELD_ALL_ADRSULN	CVD_FEM	HELD_MAL_CC	CVD_MAL	HELD_MAL_ADR	HELD_ALL_ADR	HELD_FEM_ADRSULN	HELD_ALL_ADRSULN	HELD_FEM_ADR	HELD_FEM_ADR3ULN	HELD_FEM_UEFF	HELD_FEM_LP	HELD_ALL_ADR3ULN	HELD_MAL_ADR3ULN	HELD MAL CC	HELD_ALL_CC	CVD_FEM	CVD_ALL
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BAVSNE ALLIGIBI KOLKI	. 9	Ģ	ტ	ָט	Ö	ວ :	Ð	ŋ	υ <sub>.</sub>	T :	H	Ŀ	Ţ	ı	υ	T	£.	T.	F	F	F	Ŀ
BAKSNE	5716	5716	5716	5716	2717	5717	5850	5959	6151	6236	6277	6277	6277	6277	6313	6989	6374	6374	6396	6396	6396	6396

HREQ2 B	45	14	4	23	37	70	112	9	33	101	36	56	101	34	45	12	12	0	0	85	85	88
RECUBIL	.185	130	130	95	33	. 18	116	99	125	147	78	. 82	147	120	179	246	246	78.	89	167	167	167
H. IZIS	115	. 22	72	65	35	61	114	36	82	124	19	67	124	77	112	129	129	39	34	126	126	126
TREOZ A	57	92	47	0	01	12	76	01	22	39	28	89	117	16	24	01	9	8	6	44	113	25
FREGIEN	143	24	48	14	28	16	112	28	136	53	30	20	137	136	166	98	46	48	66	20	151	27
REGISTERAL	1 <u>8</u> 8	17	<u>۳</u>	7	6	41	8	19	79	46	53	89	127	92	25	48	26	iz	54	47	132	52
III	1,28	2,67	1,85	0	0,46	8,0	0,82	2,1	0,77	1,05	1,2	1,16	E,	9,0	0,72	1,75	2,12	2,63	1,69	1,48	17	1,63
M	0,78	0,37	0,54	Time	2,16	1,25	1,22	0,48	<u></u>	36,0	0,83	98,0	60	1,66	1,38	0,57	0,47	0,38	0,59	0,68	0,83	0,61
COMPARSON	HELD ALL LIP	HELD_FEM_ADRSULN	HELD_FEM_ADR3ULN	HELD_MAL_ADRSULN	HELD MAL LIP	HELD_MAL_CC	HELD_ALL_LP	HEÇD_MAL_LIP	HELD FEM LIP	HELD_ALL_ADR3ULN	HELD_FEM_ADR3ULN	HELD_FEM_ADR	HELD_ALL_ADR	HELD FBM LIP	HELD_ALL_LIP	HELD_ALL_ADR3ULN	HELD_ALL_ADRSULN	CVD_FEM	CVD_MAL	HELD_ALL_ADR3ULN	HELD_ALL_ADR	HELD_ALL_ADRSULN (
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BATTER	7363	7.100	7409	7409	8138	8138	8138	8168	8168	8210	8210	8210	8210	8241	8241	8249	8249	8480	8480	7,128	8577	8577

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HEDRON IN		23	23	23	41	321	2	69	61	40	13	. 14	36	3 5	3 8	35	=	:	, 12	:   <u>;</u>	2, 5	34	5
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PORT TREE STEPS A STREET OF EACH	51	87	27	14	74	403	24	121	138	71	22	43	30	230	. 16	8	12	24	11/	74	103	283	-
STATES	48	47	14	7	41	315	18	96	92	22	188	23	91	139	6	24	∞	12	38	84	55	151	1
RR	<b>∄</b> ₹	0,45	0,17	0	0,58	0,84	0,53	8'0	1,28	0,73	10,1	0,46	0,28	0,85	0,43	0,77	2,69	0	5,	1,52	0,53	89,0	7
RICE	0,7	2,22	9	E E	1,74	87.	6,1	1,25	0,78	1,37	66'0	2,16	3,52 (	1,17	2,32 (	15,1	0,37 2	In	2	0,66	1,89	1,46 0	4
- COMPARISON	HELD_ALL_ADR3ULN	HELD_MAL_ADR	HELD_MAL_ADR3ULN	HELD_MAL_ADRSULN	HELD_ALL_ADR3UEN	HELD FEM LIP2	HELD FEM HDL	HELD_ALL_CC2	CVD_ALL	HELD_FEM_CC2	HELD_MAL_HDL	HELD_FEM_ADR3ULN	HELD MAL ADRIULN	HELD FEM VEFF	HELD_MAL_ADRSULN 2	HELD FEM UEFF	HELD_MAL_ADRSULN 0	HELD_MAL_CC n	HELD ALL CC	HELD_ALL_ADR3ULN 0	HELD_FEM_UEFF 1,	HELD FEM VEFF 1,	
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TAYSAR	8278	8653	8653	8653	8653	8816	8816	8816	8816	8816	8816	8931	8943	9243	. 9243	9243	9523	9940	9940	16001	10541	10541	

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	134	78	38	3	٥	=	38	01	104		551	85	271	3,4	7	:   =	117	2i9	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	61	20	. 000	143
	0	0	0	, , ,	3C .	15	124	128	382	155	723	113	357	44	2	£	163	319	2,	7.5	74	42	483
X.	25	33	19	10	2   5	13	81	89	243	59	637	66	314	35	61	08	140	269	82	47	47	25	313
	Ton I	긆	E	0.51	1 6	1,89	0,75	0,68	0,85	1,22	68'0	0,74	986	29.0	0,54	8,0	77	1,14	3,07	0,79	0,74	0,52	0,84
造	0	0	0	1 96	2	55,0	1,34	1,47	1,18	0,82	1,13	1,35	1,16	1,56	1,84		0,83	88,0	0,33	1,27 0	1,36 0	1,92	1,19 0
A CONTRACTOR OF THE PROPERTY O	CVD_MAL	HELD_ALL_HDL	HELD MAL IDL	HELD MAL LIP	HRID MAI Tro	אוח דאואי מחמני	HELD_FEM_LIP	CVD_MAL ·	HELD_FEM_LIP2	CVD_ALL	HELD_ALL_LIP2	HELD_ALL_LIP	HELD MAL LIP2	CVD_FEM	HELD_MAL_LIP	HELD FEM LIP	HELD FEM VEFF	HELD_FEM_EFF 0	CVD_FEM 0	HELD_ALL_ADR3ULN 1	HELD ALL ADRIULN	HELD_ALL_ADRSULN 1	HELD_MAL_LIP2 1,
To de la constante de la const	٧	A	A	¥	Ü		Ð	ပ	9	g	Ą	Ą	¥	¥	Y	A	U	U.	U .	U	ပ	U	J
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10600		10600	10600	1074\$	10748	10740	10/49	10785	10813	10811	10830	10830	10830	10830	10830	10830	10949	10949	10962	10962	10966	10966	11000

	KRE09 B	81	33	381	33	195	374	10	i l	33	89	<b>\$</b>	49	36	eg.	`	Ŕ	4	74	146	<u>45</u>	5	99	126	279	17
		. 29	87	1069	. 20	471	1044	19	5 8	/8	165	26	107	201	Į.		101	95	176	127		5	64	. 562	1157	95
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TOTO TOTAL		g :	9	287	6	142	280	91	16.	2	7	^	89	78	12		77	O.	57	122	1	<del>-</del>  :	2	146	294	25
Report		<b>₹</b> 9	70	97.5	6	476	096	52	28	271	3 2	3	06	134	20	22	5	51	205	154	, [5	;   2	3	478	. 296	65
Sizery	業と	3   5	3	30	2	309	620	34	12	102	¥	:   {	2	901	91	2		R R	131	138	67	:   9		715	628	42
RRJ RRS	2	<del> -</del> -	; 6	2 6	4,29	0,84	68'0	66'0	6,1	0.78	946	2 2	13.	1,19	1,42			725,0	0,81	98,0	2,43	22	-	_	1,13	1,55
R	8	15.0			÷ :	 	1,12	10'1	0,53	1.28	2.23	2, 0		28, 24	2'0	0.77			1,24 (	1,16	0,41	╌	— <u></u>	<del></del> +	0,88	0,64
COMPARISON I	CVD FEM	HELD MAL ADRUUN	HELD ALL 1.P2	HELD MAI. ADRSITIN	HEID MAI ITES	יייי ביייי	HELD_ALL_LIP2	CVD_FEM	HELD_MAL_ADR3ULN	HELD_ALL_LIP.	HELD_MAL ADRIULN	<del>-!-</del>			HELD_FEM_ADRSULN	HELD FEM ADRIULN	+-			HELD FEM VEFF	HELD MAL HDL 0	1	1	7	ארר רוויל	HELD_ALL_HDL 0,
2	၁	U	ပ	U	U	, (	ا د	د	ပ	S	T	U		1	A	¥.	E	$\dagger$	-	T	¥	A	A	A	:   <	∢
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BAYSIN	11000	11000	11000	11000	110011	11001	1001		11001	11001	11020	11073	11073	11100		11192	11248	11248.	0171	01417	11448	11448	11448	11448	11448	

REOMA SIZE B URKOL B PREOM	. 22	41	14	11	I	47	115	. 5	5.	5 .	3	17	. 61	86	205	15	19	20	10	14	15	. 20
KREOL B	114	207	99	61	79	653	1355	133	133	133	41	. £9	101	969	1239	65	17	234	106	30	43	09
SIZE B	89	124	40	36.	40	350	735	69	69	69	22	40	99	347	722	<b>6</b>	18	127	58	22	29	40
TREOS	39	3	26	17	6	89	128	4	9	11	15	20	33	124	230	6	9	-	3	10	12	16
RRI RRE STEEN FREDLY	86	061	62	21	59	995	1142	30	S6	135	47	99	93	205	1036	18	22	91	119	52	84	74
SIZEA	69	127	\$	19	*	317	635	11	31	73	31	43	63	313	633	45	14	46	19	31	48	45
ME	1,38	1,27	1,34	2,37	2,11	1,27	1,15	2,41	1,84	1,36	1,56	90,1	1,32	1,22	1,16	89'0	0,43	0,17	0,44	99'0	19'0	8,0
RR	0,73	0,79	0,75	0,42	9,48	0,79	0,87	0,41	0,54	0,73	0,64	26,0	92'0	0,82	98'0	1,48	2,35	5,88	2,29	1,52	1,49	1,24
COMPARISON THE	HELD_FEM_ADR	HELD_ALL_ADR	HELD_ALL_CC	HELD_MAL_LIP	CVD_FEM	HELD MAL LIP2	HELD_ALL_LIP2	HELD_FEM_ADRSULN	HELD_FEM_ADR3ULN	HELD FEM ADR	HELD_FEM_CC	HELD_ALL_CC	HELD_MAL_ADR	HELD_MAL_LIP2	HELD ALL LIP2	HELD_ALL_CC	HELD_MAL_CC	HELD_ALL_ADR3ULN	HELD_MAL_ADR	HELD_FEM_CC	HELD_MAL_CC2	HELD_ALL_CC
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BAYSINE ALLEGIE ALTER	Ð	Ð	<b>5</b> .	Ţ	V	9	<sub>O</sub>	L	T	Ŀ	D.	O.	∢.	4	4	4	Ö	F	Ŀ	T-	۲	L-
BAYSNR	11448	11448	11448	11450	11456	11462	11462	11483	11483	11483	11531	11536	11537	11558	11558	11558	11585	11594	11594	11614	11614	11614

		61	3.5	31	37	57	2,5	27	\$  \frac{1}{2}	6	0	8	8/	30	38	24		24	38	14	51	49	101	T
		S S	/8	28	121	171	45	201	9	36	95	70.1	727	6	22	89	89	3	178	102	. 205	63	163	101
	訓	2 2	2	25	79	114	34	74	: 65	, , ,	3 62	, 116	3	S.	104	46	46	2 3	\$	88	128	95	132	122
Teor Co		<u> </u>	2	c	22	69	27	. 4	46	2	4	2 5	3 2	10	40	26	16		•	24	4	20	32	91.
AND REPORTED FOR A TRANSPORTER	7. X	₹ ∝	, 01		101	23	E	169	74	99	122	051	3   8	77	•	0	0	202	2 6	<b>D</b> `	44	0.	25	33
SIZE	AK AK	9	1.2	- 12		98	69	203	8	3	200	8	2	:	20	13	000	32	: 5	7	42	52	<del>2</del> 8	76
RR	0.98	─+—	1 82	1 20	34.	1,33	92,0	0,78	0,82	0,41	0,77	0.79	86.0		non	null	gra	0.33	=		1 5 5	412	0,85	0,9k
K	102	33	0.55	0 7.1		0,76	1,32	1,28	1,23	2,45	15,1	1,27	1.02		5	0	0	3.06	·ļ	1	<del></del>			1,06
COMPARISON	HELD ALL HDL	HELD_MAL_ADRSULN	HELD MAL ADRUULN	HELD PEM 1.P	WET TA ATT	neld_ALL_LIF	CVD_MAL	CVD_ALL	HELD MAL ADR	HELD FEM CC	HELD FEM LIP	HELD_ALL_LIP	HELD MAL LIP	HEID ALL ADDETHAL	איירט באדי שייייי	HELD_MAL_ADR3UIN	HELD_MAL_ADRSULN	HELD ALL ADRIULN				_	-+	HELD_ALL_ADKSULN   1
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BAYSIN	11614	11631	11631	11637	11637	11633	1103/	11637	11641	11645	11646	11646	11652	12711	11727	/7/11	11727	11727	13727	11728	11914	11938	11938	

HELD_MAI_ADRSULN   0   nul
HELD_MAI_ADRSULN   0   0   0   16   55     HELD_MAI_ADRSULN   0   0   0   16   55     HELD_MAI_ADRSULN   0   0   0   16   55     HELD_MAI_ADRSULN   0   0   0   14   58     HELD_MAI_ADRSULN   0   0   0   14   58     HELD_MAI_ADRSULN   0   0   0   14   58     HELD_ALL_ADRSULN   0   0   1   0   14   58     HELD_ALL_ADRSULN   0   0   1   0   14   13     HELD_FEM_ADRSULN   0   0   1   0   14   13     HELD_FEM_ADRSULN   0   0   1   0   13   13     HELD_FEM_ADRSULN   0   0   1   0   13   13     HELD_FEM_ADRSULN   0   0   1   0   13   13     HELD_FEM_ADRSULN   0   0   0   0   0   0     HELD_FEM_ADRSULN   0   0   0   0   0   0     HELD_FEM_ADRSULN   0   0   0   0   0     HELD_FEM_ADRSULN   0   0   0   0   0     HELD_FEM_ADR   0   0   0   0   0     HELD_MAL_ADRSULN   0
HELD_MAL_ADRSULN   0   0   0   0   0   0   0   0   0
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9	99	131	SS	144	11	99	58	70,	39	59	<u>5</u> 9	129	85	- 28	58	<u>8</u>	11	139	99	35	17
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∞	16	132	62	151	17	62	17	17	\$	17	6	47	179	91	∞	47	55	148	50	3	21
2,8	1,97	1,26	1,41	1,23	1,92	0,94	96,0	1,43	1,39	1,46	127	10,1	1,06	1,48	1,36	86,0	26,0	.02	E	25,0	1,71
0,36	0,51	0,79	0,71	0,82	0,52	1,07		0,7	0,72	89,0		66,	<del>1</del>	1	<del>}</del>	<del>                                     </del>	+	<del> </del>	1-	+	0,58
HELD_MAL_ADRSULN	HELD_MAL_ADR3ULN	HELD_ALL_ADR	HELD_MAL_ADR	HELD_FEM_VEFF	HELD_FEM_ADRSULN	HELD_MAL_ADR	HELD_MAL_ADR3ULN	HELD_FEM_ADRSULN	HELD_ALL_CC	HELD_MAL_ADRSULN	THEED_MAL_ADRSUEN-	HELD_ALL_ADR3ULN	HELD MAL ADR	HELD_MAL_ADR3ULN	HELD_MAL_ADRSULN (	HELD_ALL_ADR3ULN 1	HELD FEM UEFF	HELD FEM_VEFF 0	HELD_MAL_ADR	CVD_FEM 1	HELD_PEM_VEFF 0
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12390	12399	12399	12554	12554	12851	12851	13025	13025	13191	13192	13192	13192	13192	13193	13193	13193	13338	13338	13339	13339	13340
	A G HELD_MAL_ADRSULN 0,36 2,8 8 11 5 60 106	A         Q         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         O         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         G         HELD_ALL_ADR         0,79         1,26         132         217         47         131         232	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         G         HELD_ALL_ADR         0,79         1,26         132         217    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8         60         106           A         G         HELD_ALL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           A         T         HELD_FEM_VEFF         0,82         1,23         151         234         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         71         115	A         G         HELD_MAI_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAI_ADRSULN         0,51         1,97         16         24         8         60         106           A         G         HELD_ALL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           T         C         HELD_FEM_VEFF         0,82         1,23         151         234         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         71         115           T         C         HELD_MAL_ADR         1,07         0,94         62         94         30         60         88	A         G         HELD_MAI_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAI_ADRSULN         0,51         1,97         16         24         8         60         106           A         G         HELD_MAI_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAI_ADR         0,71         1,41         62         98         26         55         99           T         C         HELD_FEM_ADRSULN         0,82         1,23         151         234         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         71         115           A         C         HELD_MAI_ADR         1,07         0,94         62         94         30         60         88           A         C         HELD_MAI_ADRSULN         1,06         0,94         17         24         10         58         80	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         G         HELD_MAL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           T         T         HELD_FEM_VEFF         0,82         1,23         151         234         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         71         115           A         C         HELD_MAL_ADRSULN         1,06         0,94         17         24         10         58         80           A         C         HELD_FEM_ADRSULN         0,7         1,43         17         19         15         70         93	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         G         HELD_MAL_ADRSULN         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           T         T         HELD_FEM_ADRSULN         0,82         1,23         151         224         68         144         243           T         C         HELD_MAL_ADR         1,07         0,94         62         94         30         60         88           A         C         HELD_MAL_ADRSULN         1,07         0,94         62         94         30         60         88           A         C         HELD_FEM_ADRSULN         0,71         1,43         17         24         10         58         80           A         C         HELD_FEM_ADRSULN         0,72         1,43         17         24	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         T         HELD_MAL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           T         T         HELD_FEM_ADRSULN         0,72         1,73         151         224         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         115         115           A         C         HELD_MAL_ADRSULN         1,05         0,94         62         94         30         60         88           A         C         HELD_FEM_ADRSULN         0,71         1,43         17         19         15         70         93           G         A         HELD_MAL_DALL_CC         0,72         1,39         43         50	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         A         G         HELD_MAL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           T         T         HELD_FEM_ADRSULN         0,52         1,23         17         224         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         71         115           A         C         HELD_MAL_ADRSULN         1,07         0,94         62         94         30         60         88           A         C         HELD_FEM_ADRSULN         0,7         1,43         17         24         10         36         39         58           T         C         HELD_MAL_ADRSULN         0,7         1,43	A         Q         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         Q         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         Q         HELD_MAL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           T         T         HELD_FEM_ADRSULN         0,52         1,52         17         224         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         71         115           A         C         HELD_MAL_ADRSULN         1,07         0,94         62         94         30         60         88           A         C         HELD_MAL_ADRSULN         0,71         1,43         17         24         10         53         9         53           T         C         HELD_MAL_ADRSULN         0,72         1,43         17	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRR         0,79         1,97         16         24         8         60         106           A         G         HELD_MAL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           T         C         HELD_FEM_ADRSULN         0,52         1,22         17         22         17         115         115         115         11         115         115         115         115         115         115         11         115         115         115         11         115         115         115         115         115         115         115         115         115         115         115         115         115         115         115         115         115         115	A         G         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    17         24         10         58         9         59         77	A         Q         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106         14           A         Q         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106         14           A         Q         HELD_ALL_ADR         0,79         1,26         132         217         47         131         232         30           A         T         HELD_ALL_ADR         0,71         1,41         62         98         26         55         99         11           A         T         HELD_FEM_VEFF         0,82         1,23         151         21         68         144         243         45           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         71         115         27           A         C         HELD_MAL_ADRSULN         1,03         62         94         30         60         88         32           A         C         HELD_MAL_ADRSULN         0,72         1,43         17         24         10         59         59         59         59         50	A   G   HELD_MAL_ADRSULN   0,36   2,8   8   11   5   60   106   14     A   G   HELD_MAL_ADRSULN   0,51   1,97   16   24   8   60   106   14     A   G   HELD_ALL_ADR   0,79   1,26   132   217   47   131   232   30     A   T   HELD_MAL_ADR   0,71   1,41   62   98   26   55   99   11     A   T   HELD_FRA_VEFF   0,82   1,23   151   224   68   144   243   45     T   C   HELD_FRA_ADRSULN   0,52   1,92   17   22   12   71   115   27     A   C   HELD_MAL_ADRSULN   1,06   0,94   17   24   10   58   80   36     A   HELD_MAL_ADRSULN   0,7   1,43   17   19   15   70   93   47     T   C   HELD_MAL_ADRSULN   0,7   1,43   17   19   15   70   93   47     T   C   HELD_MAL_ADRSULN   0,7   1,43   17   19   15   17   129   51     T   C   HELD_MAL_ADRSULN   0,8   1,46   17   25   9   59   59   51     T   C   HELD_MAL_ADRSULN   0,98   1,06   61   88   24   59   59     T   C   HELD_MAL_ADRSULN   0,98   1,06   61   88   24   59   59     T   C   HELD_MAL_ADRSULN   0,94   1,06   61   88   24   59   59     T   C   HELD_MAL_ADRSULN   0,98   1,48   16   23   9   75   71     G   A   HELD_MAL_ADRSULN   0,48   1,48   16   23   9   75   71     G   A   HELD_MAL_ADRSULN   0,74   1,36   8   12   4   58   94   22     G   A   HELD_MAL_ADRSULN   0,74   1,36   8   12   4   58   94   22     G   A   HELD_MAL_ADRSULN   0,78   1,71   17   130   212   48     G   A   HELD_MAL_ADRSULN   0,78   1,71   17   17   130   212   48     G   A   HELD_MAL_ADRSULN   0,74   1,36   8   12   7   7   7   7   7   7   7   7   7	A         Q         HELD_MAL_ADR3ULN         0,36         2,8         8         11         5         60         106         14           A         Q         HELD_MAL_ADR3ULN         0,79         1,87         16         24         8         60         106         14           A         Q         HELD_MAL_ADR         0,79         1,26         132         217         47         131         232         30           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           T         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         35         99         11           T         C         HELD_MAL_ADR         1,07         0,94         62         94         30         60         88         32           A         C         HELD_MAL_ADR3ULN         1,05         6,94         17         24         10         38         36         39         36           A         C         HELD_MAL_ADR3ULN         0,71         1,43         17         14         17         17         17         <	A         Q         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106         14           A         Q         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106         14           A         Q         HELD_ALL_ADR         0,71         1,47         62         29         26         35         99         11           A         T         HELD_ALL_ADR         0,71         1,41         62         98         26         35         99         11           A         T         HELD_MAL_ADR         0,71         1,41         62         94         36         45         17           T         C         HELD_MAL_ADR         1,07         0,94         17         24         10         58         80         36           A         C         HELD_MAL_ADRSULN         1,07         0,94         17         24         10         58         9         59         9         7           T         C         HELD_MAL_ADRSULN         1,07         1,43         17         14         24         38         20         9         14 </th <th>  A   Q   HELD_MAL_ADRSULN   0,21   197   16   24   8   11   5   60   106   14     A   G   HELD_MAL_ADRSULN   0,21   197   16   24   8   60   106   14     A   T   HELD_ALL_ADR   0,71   1,41   62   58   59   11     A   T   HELD_MAL_ADRSULN   0,82   1,23   151   234   68   144   243   45     T   C   HELD_MAL_ADRSULN   0,82   1,92   17   24   10   58   80   35     A   C   HELD_MAL_ADRSULN   0,04   17   24   10   58   80   36     A   C   HELD_MAL_ADRSULN   0,07   1,43   17   19   15   10   58   80   36     T   C   HELD_MAL_ADRSULN   0,07   1,43   17   19   15   10   59   59   59     T   C   HELD_MAL_ADRSULN   0,08   1,46   17   24   10   58   59   59     T   C   HELD_MAL_ADRSULN   0,08   1,46   17   24   17   129   212   46      T   C   HELD_MAL_ADRSULN   0,08   1,46   17   25   9   59   59   59      T   C   HELD_MAL_ADRSULN   0,08   1,46   17   17   129   212   46      T   C   HELD_MAL_ADRSULN   0,08   1,48   16   23   9   59   59   59      T   C   HELD_MAL_ADRSULN   0,08   1,48   16   23   9   59   59      G   A   HELD_MAL_ADRSULN   0,08   1,48   16   23   9   59   59      G   A   HELD_MAL_ADRSULN   0,08   1,48   16   23   9   59   59      G   A   HELD_MAL_ADRSULN   0,08   1,48   16   23   9   59   59      G   A   HELD_MAL_ADRSULN   0,08   1,48   16   23   9   59   59      G   A   HELD_MAL_ADRSULN   0,08   1,48   16   23   9   59   59      G   A   HELD_MAL_ADRSULN   0,08   1,48   16   23   9   59   59      G   A   HELD_MAL_ADRSULN   0,08   1,48   16   23   9   59   59      G   A   HELD_MAL_ADRSULN   0,08   1,48   16   10   10   10   10   10   10   10</th> <th>  A   Q   HELD_MAL_ADRSULN   Q.54   Q.54   B   11   S   60   1166   14     A   Q   HELD_MAL_ADRSULN   Q.71   1,57   16   24   8   60   106   14     A   T   HELD_MAL_ADRSULN   Q.71   1,41   62   98   26   55   99   11     A   T   HELD_FEM_ADRSULN   Q.72   1,22   17   22   12   17   115   23   45     T   C   HELD_FEM_ADRSULN   Q.72   1,22   17   22   12   11   115   27     A   C   HELD_MAL_ADRSULN   Q.72   1,24   10   58   80   36   36     A   C   HELD_MAL_ADRSULN   Q.71   1,41   24   10   58   80   36     A   C   HELD_MAL_ADRSULN   Q.71   1,43   17   19   15   70   93   47     A   C   HELD_FEM_ADRSULN   Q.72   1,29   43   50   50   60   88   32    A   C   HELD_MAL_ADRSULN   Q.72   1,29   43   50   50   50   50    A   HELD_MAL_ADRSULN   Q.72   1,20   47   77   17   17   17   17    A   C   HELD_MAL_ADRSULN   Q.72   1,48   16   23   9   59   57   21    A   C   HELD_MAL_ADRSULN   Q.72   1,48   16   23   9   58   59   57    A   C   HELD_MAL_ADRSULN   Q.72   1,48   16   23   9   58   59   57    A   HELD_MAL_ADRSULN   Q.72   1,48   16   23   9   58   59    A   HELD_MAL_ADRSULN   Q.72   1,48   16   23   9   58   59    A   HELD_MAL_ADRSULN   Q.72   1,48   15   70   9   13   17   17    A   HELD_MAL_ADRSULN   Q.73   1,48   16   23   35   35   35    A   HELD_MAL_ADRSULN   Q.73   1,48   187   109   139   178   100    A   HELD_MAL_ADRSULN   Q.73   1,48   187   109   139   178   100    A   HELD_MAL_ADRAU_BER   Q.73   1,48   187   109   139   178   100    A   HELD_MAL_ADRAU_BER   Q.73   1,48   187   109   139  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	1,47	89,1	1,33	n n	1,23	0,67	1,14	1,14	16'0	0,87	1,18	1,09	85,1	1,29	1,35	0,85	0,88	=	10,1	1,17	1,29	1,29
	89'0	0,59	0,75	0	0,81	1,5	0,87	0,87	1,1	1,15	0,85	0,92	0,73	11/0	0,74	1,18	1,14	16'0	0,99	0,86.	0,77.	0,77
COMPARISON :	HELD FEM USFF	HELD FEM ADRIULN	HELD_FEM_ADR	HELD_MAL_ADRSULN	HELD_FEM_EFF	HELD_FEM_ADR	HELD FEM EFF	HELD_FEM_EFF	HELD MAL ADRSULN	HELD FEM BFF	HELD_FEM_EFF	HELD REM VEFF	HELD FEM DEFF	HELD_ALL_ADR3ULN	HELD_MAL_ADR3ULN	HBLD_FEM_EFF	HELD_ALL_ADRSULN	HELD_ALL_ADR3ULN	HELD_FEM_ADRSULN	HELD FEM ADROULN	HELD_ALL_ADR	HELD_FEM_ADR
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RIC	0,34	0,31	1,04	1,23	2,01	92,0	0,62	0,76	2,45	0,75	1,33	0,62	0	0	0	THE STATE OF	1,51	1,24	0,47	1,35	1,35	1,67
HHI	1,85	1,24	96,0	0,81	강	15,1	1,62	1,32	0,41	£,1	0,75	1,62	Inn	ם	THE STATE OF	0	99'0	0,81	2,11	0,74	0,74	9,0
COMPARISON OF	HELD_FEM_ADR3ULN	HBLD_MAL_ADR	HELD_ALL_ADR	HELD_FEM_ADR	HELD_FEM_ADRSULN	HELD FEM EFF	HELD_FEM_UEFF	HBLD_FEM_VEFF	HELD_MAL_ADRSULN	HELD_MAL_ADR	HELD FEM ADR	HELD FEM VEFF	HELD_ALL_ADRSULN	HELD_MAL_ADRSULN	HELD_FEM_ADRSULN	HELD_MAL_ADRSULN	HELD_ALL_ADR3ULN	HELD_FEM_VEFF	HELD MAL ADRIULN	HELD FEM UEFF	HELD_FEM_ADR	HELD FEM ADR3ULN
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Na.	0,7	0,58	0,82	1,57	1,77	Time	0,71	0,57	0,84	0,53	0,73	96.0	.   8	9,	£6'0.	0	0	1,86	1:1	+-	99'0		-	-
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T. C.	7,65	1,21	0,52	0,77	1,00	0,47	80	0,97	0,77	0,82	1,26	1,63	0,32	0,79	0,62	0,79	0,86	0,66	0,38	1,29	2,04	0,97
	19'0	0,83	1,91	1,29	1,42	2,13	0,93	1,03	1,3	1,23	0,79	190	3,15	1,26	1,62	1,26	1,17	1,52	2,61	0,78	0,49	1,04
CONRANISON HIS	HELD_ALL_ADR3ULN	HELD_ALL_ADR	HELD_FEM_UEFF	HBLD_FEM_EFF	HELD_FEM_VEFF	HELD_ALL_ADR5ULN	HELD_FEM_VEFF	HELD FEM UEFF	CVD_ALL	CVD_MAL	HELD FEM UEFF	HELD_FEM_ADR3ULN	HELD_MAL_ADR3ULN	RELD_FEM_EFF	HELD_FEM_UEFF	HELD_FEM_VEFF	HELD FBM EFF	HELD FEM UEFF	HELD_MAL_ADR3ULN	HELD MAL ADR	HELD MAL ADR3ULN	HELD FEM VEFF
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	1,53	1,68	2,56	77	0,94	2,51	2,27	2,52	1,55	2,14	1,93	7,7	2,39	1,21	1,21	1,29	-	96'0	1,55	1,07	0,99	0,79	
	99'0	0,59	65,0	5,0	1,07	4,0	0,44	6,0	0,64	0,47	0,52	0,13	0,42	0,83	0,83	0,78	-	1,94	0,64	0,94	1.0	1,27	
COMPARISON	HELD ALL ADROUEN	HELD_ALL_ADRSULN	HELD MAL ADRIULN	HELD_ALL_ADRSULN	CVD_FEM	HELD MAL ADRSULN	HELD_ALL_ADRSULN	HELD_MAL_ADR3ULN	HELD ALL ADRICEN	HELD FEM ADRSULN	HELD_ALL_ADRSULN	HELD MAL ADRSULN	HELD_MAL_ADRUUN	HELD_ALL_ADR	HELD ALL ADRIULN	HELD FEM ADR	HELD FEM VEFF	HELD FEM EFF	RELD_FEM_UEFF	HELD_MAL_ADR	HELD_ALL_ADR	CVD_MAL	
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	0,7	0,89	0,85	0,69	0,5	1,32	0,93	0,47	0,42	55,1	1,23	84,	1,2	3,44	1,6	1,47	1,12	0,81	1,28	0,88	Han	Tal	1
PENCONFARSON	HELD FEM ADR	HELD_FEM_VEFF	HELD_FEM_UEFF	HBLD_MAL_ADR	HBLD_MAL_ADR3ULN	HELD_ALL_ADRSULN	HELD MAL ADRSULN	HELD FEM ADROULN	HELD FEM ADRSULN	HELD FEM UEFF	HRLD_FEM_VBFF	HBLD_FEM_UEFF	HELD FEM VEFF	HELD_MAL_LIP	HELD_FEM_BFF	HELD_FEM_VEFF	HELD_FEM_ADRSULN	HELD_ALL_ADRSULN	HELD FEM EFF	HELD FEM EFF	HELD_ALL_ADR	HELD FEW ADR	
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	1,13	6,83	0	0	0,65	0	1.93	0,84	0,82	0,55	0,47	2,08	0,37	5,0	-	0,69	1,71	0,84	1,112	1,22	0,28	Tiggi Tiggi
	0,89	1,21	Igna	Fina	1,55	IM.	0,52	1,19	121	1,83	2,12	0,48	2,71	2,02	-	1,44	0,58	1,19	60	0,82	3,59	0
COMPARISON	RELD_FEM_BFF	HELD_FEM_ADR	CVD_FEM	HELD_ALL_ADRSULN	CVD_FBM	HELD_ALL_ADRSULN	HELD_FEM_ADRSULN	HELD FEM CC	HELD MAL ADR	HELD ALL ADRIGH	HELD FEM ADRIULN	HELD MAL LIP	HELD FEM LIP	HELD FEM ADRAULN	CVD_FBM	CVD_ALL	CVD_FEM	HELD FEM EFF	HELD_FEM_EFF	CVD_MAL	HELD_FEM_ADR	HELD_ALL_ADRSULN
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## **Claims**

1. An isolated polynucleotide encoded by a phenotype associated (PA) gene; the polynucleotide is selected from the group comprising

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SEQ ID 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292 with allelic variation as indicated in the sequences section contained in a functional surrounding like full length cDNA for PA gene polypeptide and with or without the PA gene promoter sequence.

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2. An expression vector containing one or more of the polynucleotides of claim 1.

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A host cell containing the expression vector of claim 2.

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- 4. A substantially purified PA gene polypeptide encoded by a polynucleotide of claim 1.
- 5. A method for producing a PA gene polypeptide, wherein the method comprises the following steps:
  - a) culturing the host cell of claim 3 under conditions suitable for the expression of the PA gene polypeptide; and
- b) recovering the PA gene polypeptide from the host cell culture.
  - 6. A method for the detection of a polynucleotide of claim 1 or a PA gene polypeptide of claim 4 comprising the steps of:
- contacting a biological sample with a reagent which specifically interacts with the polynucleotide or the PA gene polypeptide.
  - 7. A method of screening for agents which regulate the activity of a PA gene comprising the steps of:
- contacting a test compound with a PA gene polypeptide encoded by any polynucleotide of claim 1; and detecting PA gene activity of the polypeptide, wherein a test compound which increases the PA gene polypeptide activity is identified as a potential therapeutic agent for increasing the activity of the PA gene polypeptide and wherein a test compound which decreases the PA activity of the polypeptide is identified as a potential therapeutic agent for decreasing the activity of the PA gene polypeptide.
  - 8. A reagent that modulates the activity of a PA polypeptide or a polynucleotide wherein said reagent is identified by the method of the claim 7.

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- A pharmaceutical composition, comprising:
   the expression vector of claim 2 or the reagent of claim 8 and a pharmaceutically acceptable carrier.
- 5 10. Use of the reagent according to claim 8 for the preparation of a medicament.
- 11. A method for determining whether a human subject has, or is at risk of developing a cardiovascular disease, comprising determining the identity of nucleotide variations as indicated in the sequences section of SEQ ID 1-292 of the PA gene locus of the subject and where the SNP class of the SNP is "CVD" as can be seen from table 3; whereas a "risk" genotype has a risk ratio of greater than 1 as can be seen from table 6.
- 12. A method for determining a patient's individual response to statin therapy, including drug efficacy and adverse drug reactions, comprising determining the identity of nucleotide variations as indicated in the sequences section of SEQ ID 1-292 of the PA gene locus of the subject and where the SNP class of the SNP is "ADR", "EFF" or both as can be seen from table 3; whereas the probability for such response can be seen from table 6.

- 13. Use of the method according to claim 12 for the preparation of a medicament tailored to suit a patient's individual response to statin therapy.
- 14. A kit for assessing cardiovascular status or statin response, said kit comprising
  - a) sequence determination primers and
  - b) sequence determination reagents,

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wherein said primers are selected from the group comprising primers that hybridize to polymorphic positions in human PA genes according to claim 1; and primers that hybridize immediately adjacent to polymorphic positions in human PA genes according to claim 1.

- 15. A kit as defined in claims 12 detecting a combination of two or more, up to all, polymorphic sites selected from the groups of sequences as defined in claim 1.
- 16. A kit for assessing cardiovascular status or statin response, said kit comprising one or more antibodies specific for a polymorphic position defined in claim 1 within the human PA gene polypeptides and combinations of any of the foregoing.

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Single Nucleotide Polymorphisms as Predictive Diagnostics for Adverse Drug Reactions (ADR) and Drug Efficacy

## Abstract

The invention provides diagnostic methods and kits including oligo and/or polynucleotides or derivatives, including as well antibodies determining whether a human subject is at risk of getting adverse drug reaction after statin therapy or whether the human subject is a high or low responder or a good a or bad metabolizer of statins. The invention provides further diagnostic methods and kits including antibodies determining whether a human subject is at risk for a cardiovascular disease. Still further the invention provides polymorphic sequences and other genes.

#### SEQUENCE LISTING

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- 14 -

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900.

960

1001

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5.28

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S.30

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360

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Le A 36 562

- 81 -

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Homo Sapiens

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Homo Sapiens

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- 116 -

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960

1001

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TIN TO LEVERKUSEN

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1

THE LEVERKUSEN

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Homo Sapiens

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BHYER AG LEVERKUSEN

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S.35

- 138

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Homo Sapiens

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